INTERNATIONAL RECORD OF MEDICINE

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SYMPOSIUM ON THE MECHANISM AND MANAGEMENT OF HEMORRHAGIC DISORDERS IN CHILDREN

PART I

GUEST EDITOR—I. NEWTON KUGELMASS, M.D., PH.D., SC.D.

Introduction — I. NEWTON KUGELMASS

Mechanism of Hemostasis — L. B. JAQUES

Disorders of the Hemostatic Mechanism — GEORGE D. PENICK AND WILLIAM W. McLENDON

Diagnostic Procedures in Hemorrhagic Diseases of Children — JEANETTE SCHULZ

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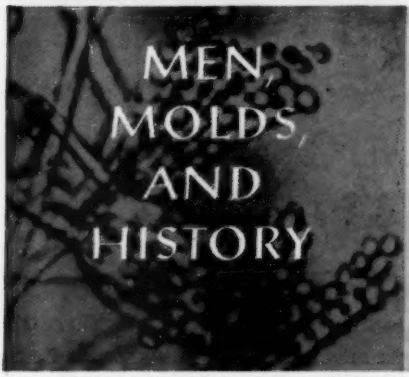

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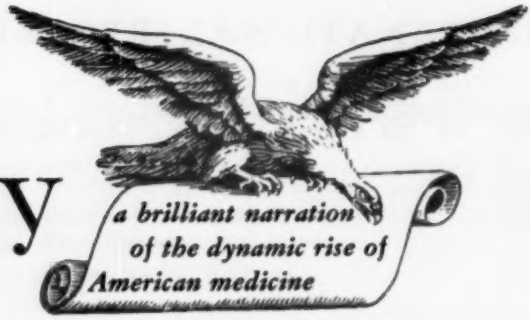

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Symposium on the Mechanism and Management of Hemorrhagic Disorders in Children

Part I

GUEST EDITOR—I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D.

Introduction

I. Newton Kugelmass, M.D., Ph.D., Sc.D.

CONSULTANT TO THE DEPARTMENTS OF HEALTH AND HOSPITALS, NEW YORK CITY

NEW YORK, N. Y.

Our newer knowledge of the blood-clotting mechanism provides a clearer yet more complex picture of the fundamental process, but destroys the clinical illusion of its chemical simplicity. Blood coagulation involves a highly integrated system of interacting accelerators and inhibitors rather than a simple enzymatic modification of fibrinogen. Clinical recognition of heredofamilial hemorrhagic syndromes caused by defects in factors, cofactors, accelerators, activators, and inhibitors makes possible early and accurate identification by specific laboratory procedures. Hemorrhagic disorders are far more prevalent than was previously assumed—hence the need for detecting mild, ill-defined bleeding problems by methods based on the three phases of blood clotting—proceeding simultaneously at different rates.

Bleeding in hemorrhagic disease may be spontaneous or traumatic as a result of vascular weakness, defective or deficient platelets, or faulty blood clotting. Vascular or clotting defects must be suspected in the presence of unexplained hemorrhage of any type or in any location. Because there are multiple causes of hemorrhagic disorders, critical laboratory studies are required to identify the underlying basis of the condition. Several tests of clotting function by bedside and laboratory methods will disclose most of the hemorrhagic diseases, but special procedures are necessary for identification of the rare hereditary disturbances.

In this symposium, Dr. Jaques of Saskatchewan clarifies the mechanism of hemo-

Part II of this Symposium will appear in the September issue.

stasis. The clot was always thought to be a mechanical plug in the arrest of bleeding, but recent studies have brought to light more determining factors in the lifesaving process.

Drs. Penick and McLendon of Chapel Hill, North Carolina, interpret the pathogenesis of hemorrhagic disease in terms of body imbalances in the physiological response to injury. Hemorrhage thus occupies a position at one end of the spectrum and thrombosis at the other.

Dr. Schulz of Los Angeles presents the clinical interpretation of modern diagnostic procedures in the evaluation of hemorrhagic diseases of children.

Dr. Douglas of Glasgow evaluates the magnitude of the therapeutic problem in hereditary hemorrhagic disorders in view of the nonavailability of large quantities of concentrated preparation of antihemophilic globulin, plasma thromboplastin component, and other specific clotting components, but presents an effective approach not only in the management of an acute hemorrhage but in the presence of bleeding episodes.

Drs. Hardisty and Ingram of London present the clinical and laboratory methods of investigating a genetic bleeding problem in childhood in terms of plasma hemostatic components and family patterns as a basis for specific prophylactic and therapeutic measures, local and systemic, in the light of our recent advances.

Dr. Kugelmass of New York applies these methods in establishing the pertinent features of each group of hemorrhagic diseases evolved from each clotting component and formulates specific therapeutic measures indispensable for everyday practice.

Dr. de Nicola of Pavia, Italy, introduces a new diagnostic procedure, thromboelastography, which makes possible the measurement of the physical properties of the clot during its formation with particular reference to adhesiveness, resistance, and elasticity in hemorrhagic diseases involving clot defects.

Drs. Rodman and Pastor of Philadelphia offer a safe and effective anticoagulant program for the prevention and treatment of thromboembolic diseases by administering heparin, coumarin, and indanedione.

The mechanism of hemorrhagic disorders can only be unraveled from the nature of blood coagulation. It is now only partially understood for many factors are yet to be explained. The future promises much for the clarification of the role of blood coagulation factors, the isolation of fibrinolytic and anticoagulant agents, and the better understanding of hemostasis, the lifesaving mechanism of the body in health and disease.

Mechanism of Hemostasis

L. B. Jaques, M.A., Ph.D., F.R.S.C.

PROFESSOR AND HEAD OF THE DEPARTMENT OF PHYSIOLOGY AND PHARMACOLOGY, UNIVERSITY OF SASKATCHEWAN
SASKATOON, SASKATCHEWAN, CANADA

BASIC DESCRIPTION OF HEMOSTASIS

With the development of a circulating fluid moving under pressure, the loss of such fluid at any time represents mortal danger to the organism. It is therefore not surprising that there has evolved a series of complex mechanisms necessary for protection against such danger. These mechanisms we describe by the term "hemostasis" or the stopping of bleeding. The mechanisms involved are: the coagulation of blood or formation of fibrin, the clumping of platelets or formation of a plug, and the reaction and integrity of the blood vessel wall. Basic to the effectiveness of these mechanisms is blood flow, since on the one hand it brings materials necessary for hemostasis and on the other hand it will wash away a partly or poorly formed block. We can list this as a fourth factor in determining hemostasis.

BLOOD COAGULATION OR FIBRIN FORMATION

Present in the plasma in solution is fibrinogen. The enzyme thrombin splits off peptide from the protein thus making available chemical groups on the fibrinogen molecules, which combine to build up a protein fiber. These fibers, interlacing, form a gel structure. The gel has rigidity or tensile strength and as a result the blood becomes solid. For adequate gel strength the fiber formation must be very rapid. In the circulation the flowing blood will interfere with gel formation and therefore fibrin formation must be even more rapid. Thrombin is present in the blood in an inactive form, prothrombin. Prothrombin is converted to thrombin in the presence of calcium ions with the aid of a number of activators; the conversion takes place in several steps involving degradation and marked changes in the prothrombin protein. For the activation of prothrombin, the most effective agent and the one that is generally the initiator of clotting is the thromboplastin liberated from damaged tissue. Under certain conditions, notably contact with glass, a similar activity develops in blood (evolution of plasma thromboplastin). Present in blood and plasma is a fibrinolytic mechanism, due to an enzyme, plasmin. Normally this enzyme is present in plasma in an inactive form, plasminogen. Various factors including substances from tissue can cause activation of plasminogen and produce an active enzyme that will cause very rapid destruction of fibrinogen and fibrin.

PLATELETS OR PLATELET PLUG FORMATION

The platelets are formed from the megakaryocytes in the bone marrow and circulate as discrete objects 1 to 4 μ in diameter. However, when they come into contact with any foreign material or damaged tissue, they stick to it and to each other and

in this way build up a plug of material that will effectively seal small breaks in blood vessels—the *clou hémostatique*.

REACTION AND INTEGRITY OF THE VESSEL WALL

The integrity of the vessel wall depends particularly on the cement substance between the cells of the endothelium. This is affected by a great many physiological factors, various hormones and vitamins. The substance is constantly being renewed. Since this is the site where leukocytes pass out from the endothelium into the tissue spaces, if there is any defect in the replacement of the cement substance, red cells will pass out also and there will be actual bleeding into tissues. Vessels will respond to damage by vasoconstriction. This applies to all vessels down to the capillaries. In the case of the capillaries, the precapillary sphincter by constricting will stop any flow of blood through the damaged capillary and thus prevent blood loss through it. Various vasoconstrictor agents such as adrenaline and serotonin are an important part of the hemostatic mechanism.

INTERACTION OF MECHANISMS

While it is convenient to examine these three mechanisms separately, it must be understood that they interact and reinforce each other. The clotting system, by formation of fibrin, ties platelet clumps together and thus makes this mechanism more effective. Fibrin deposition on endothelium probably reinforces the integrity at a point that has been damaged. Platelets adsorb various substances and serve to transport them in the circulation. Among these are activators for the blood coagulation system and adrenaline and serotonin, which reinforce the vascular mechanism. The damage of platelets as they adhere or stick to a damaged blood vessel releases these agents, and the accumulation of platelets concentrates these agents at the damaged area. Vasoconstriction by impeding blood flow will also assist the coagulation and platelet mechanisms in their hemostatic function.

COAGULATION TESTS AND CLINICAL BLEEDING

Various simple coagulation tests illustrate how different mechanisms of hemostasis are deranged in hemorrhagic diseases. The clotting time is quite prolonged or is absent if there is no fibrinogen and quite prolonged in the hemophilias. The prothrombin time is found to be normal (12 seconds) in hemophilia, etc., prolonged on treatment with bishydroxycoumarin. The bleeding time is normal in hemophilia, afibrinogenemia, etc., but is prolonged in the purpuras. This illustrates that there is a difference in the type of bleeding with the different types of defect in the hemostasis. Deficiencies in vascular integrity can be tested for by measurement of capillary fragility or resistance. The breaking pressure of the capillaries is found to be very low with adrenalectomy, reduced during menstruation, elevated immediately after stress, lowered with prolonged stress. Normal functioning of platelets can be checked by the prothrombin utilization test. Factors such as antihemophilic globulin, which assist the formation of plasma thromboplastin, can be checked by the thromboplastin generation test.

The type of clinical bleeding also varies with the mechanism affected. Conditions associated with defects in the coagulation system show the same type of symptoms or bleeding—bleeding from bruises where larger vessels are torn, bleeding into the joints, and intractable bleeding after tooth extraction and similar procedures. Defects in platelet and vascular mechanisms result in purpura. Such bleeding can be not only in the skin but in internal organs such as the liver.

HEMORRHAGE AND THROMBOSIS

The control of hemorrhage requires an understanding of the nature of the defects that have developed and how they may be corrected. Underactivity of hemostatic mechanisms may result in hemorrhage, elicited by trauma, and this may occur even in the apparently normal subject. However, serious spontaneous hemorrhage does not occur even though one of the hemostatic mechanisms is absent through inheritance or disease. The other mechanisms will still be sufficient. The hemophilic person

TABLE I

Production of Spontaneous Hemorrhage (from Jaques et al [1, 5, 7])

Treatment	Known effect of treatment	Bishydroxy-coumarin	Heparin	Reserpine	Stress	Adrenalectomy
		Death from spontaneous hemorrhage				
Bishydroxy-coumarin	Anti-coagulant	− B.C.	−	+	+	+
Heparin	Anti-coagulant*	B.C.; B.C.	− B.C.	+	−	+
Reserpine	Removes platelet serotonin	P.; B.C.	P.; B.C.	− P.	+	+
Frostbite						
10 Per cent sodium chloride, intraperitoneal	Low capillary resistance	V.I.; B.C.	• V.I.; B.C.	V.I.; P.	− V.I.	−
Insulin						
Adrenalectomy						
ACTH	Low capillary resistance	V.I.; B.C.	V I.; B.C.	V.I.; P.	V.I.; V.I.	− V.I.
		Hemostatic mechanisms affected				

B.C. = Blood coagulation; P. = platelets; V.I. = vascular integrity.

* Interferes with stress mechanisms.

does not bleed continually. Anticoagulants do not cause bleeding in the normal person. It is only if several of the hemostatic mechanisms are interfered with that hemorrhage is very difficult to control. In table I are shown the results[1] of various treatments that caused death from spontaneous hemorrhage in rats or rabbits (+ means mortality of 50 to 100 per cent; − means negligible mortality from spontaneous hemorrhage). Treatments are listed along the side and across the top of the table. It will be observed that along the diagonal, which represents single treatments, the results are negative. Where treatments were given in combination, there was frequently high mortality from hemorrhage. This is clarified in the lower left-hand part of the table. Here are entered the hemostatic mechanisms affected by the treatments. Hemorrhage resulted when both coagulation and platelets, or both coagulation and blood vessels, or both platelets and blood vessels were affected. Neither treatment with anticoagulants nor stress caused hemorrhage. Together they caused hemorrhage and resultant death.

Overactivity of hemostatic mechanisms in the body can lead to intravascular clotting or thrombosis. The factors involved are summarized in Virchow's triad: changes in chemistry of the blood, damage to the vessel wall, and stasis. Or, if we divide Virchow's first postulate into the coagulation system and platelets, we have the same four factors we have already seen active in determining hemorrhage. Platelets adhering to a damaged portion of the vessel wall will pile up and form a white thrombus. This is followed first downstream and then upstream by formation of a solid clot, so that the vessel is completely blocked. Since anticoagulants prevent the clotting of blood either directly or indirectly, it was early suggested that they might affect thrombosis. The demonstration of this with heparin in 1934[2] led to the introduction of anticoagulant therapy for thrombosis clinically. But just as with hemorrhage, it has been found experimentally that there must be multiple changes in the factors in order for thrombosis to occur.

CLINICAL FACTORS TENDING TO PRECIPITATE HEMORRHAGE OR THROMBOSIS

Factors that cause changes in hemostatic mechanisms by either decreasing or enhancing the action of any component are listed in table II. They are grouped in terms of affecting the first, second, and third stages of coagulation, platelets, or blood vessel wall. Any of those listed as decreasing factors can contribute to hemorrhage, but as emphasized previously, none of them singly can be a cause; similarly for the factors listed as contributing to counteracting hemorrhage or the precipitation of thrombosis. It is the sum or total of changes from the golden mean of hemostasis that determines whether spontaneous hemorrhage (or thrombosis) occurs in a given patient. As can be seen in table II, the same agent (stress, abdominal surgery) appears in a number of places. There can then even be some canceling out of effect, and this explains such paradoxes as the relatively low incidence of hemorrhage in the newborn infant in spite of the low levels of prothrombin. An attempt has been made not only to classify the various changes in hemostatic mechanisms that can and do occur, but to indicate the pathways leading to such changes. While there is an enormous literature giving this information in the case of changes in coagulation

and in platelets, for the blood vessel component of hemostasis, this information depends largely on Roskam,[3] Kramár,[4] and ourselves.[5]

When large amounts of thromboplastin enter the circulation, the blood frequently becomes incoagulable. This paradoxical result is due to the fact that, instead of forming an intravascular clot, as the fibrin forms in the flowing blood, it is deposited on the vessel walls as fibrin threads, leaving the circulating blood incoagulable. Such entry of thromboplastin occurs particularly in abruptio placentae, from the intervillous lake. It is possible for the fibrin as formed to provide emboli, and this is a significant factor in eclampsia.[6] The levels of factors V, VII, X, and fibrinogen are most sensitive indicators of hepatic function. Simple operative manipulation causes a fall in factor VII and X levels, while plasma fibrinogen levels are a more sensitive indicator of pyrogens than the body temperature. Normally, there are only traces of the tissue components thromboplastin and heparin in the blood. However, shifts in body fluids from tissues to blood (when digitalis or diuretics are used) increase the amount of thromboplastin reaching the general circulation. Plasma antibodies are particularly significant as hemorrhagic factors with respect to antihemophilic globulin and as platelet agglutinins. Often overlooked is the fact that when materials are introduced intravenously, a transient thrombocytopenia lasting 30 or 40 minutes frequently results, due to the temporary agglutination of platelets and the sieving out of the clumps in capillary beds. Since the platelet count is back to normal by the time a blood sample is ordered, purpura and other symptoms cannot be explained. The increased platelet stickiness or increased activity that accompanies the postoperative thrombocytosis is a reflection of the relatively greater numbers of young platelets in the circulation at that time.

Changes in the blood vessels are elicited by many factors of common clinical occurrence. This mechanism is much more responsive in both degree and speed to neurological and humoral factors than blood coagulation or blood platelets. Hence, it is this pathway that chiefly determines the occurrence of spontaneous hemorrhage at a particular time in the light of the patient's case history. Methods of studying this mechanism have included determination of capillary resistance (capillary fragility), bleeding time, biomicroscopy of vessels, and mortality (as the result of multiple hemostatic deficiencies). There has been much criticism of the first two methods on the grounds of lack of reproducibility. However, these critics have overlooked the fact that if they cannot find a physical cause of the nonreproducibility, they must be overlooking and failing to control the biological variable of significance in the test. Measurable changes in capillary resistance (fragility) can be detected in less than a minute after producing pain. This may be an important protective mechanism against hemorrhage, since in contrast to coagulation and platelets, changes in capillary resistance to increase hemostatic effectiveness above normal occur quickly and readily. A profound decrease in capillary resistance occurs in women during menstruation. We have been greatly impressed to observe in experimental animals how increased permeability over several days can give a clinical picture typical of severe hemorrhage. It is the loss of blood (whether over the whole inner surface of the vascular system or at a single point) that is responsible for the clinical syndrome.

TABLE II

Factors Decreasing and Increasing Hemostatic Mechanisms

Hemostatic mechanism affected	Decreasing factors			Increasing factors		
	Nature of change	Pathway	Produced by/occurs in	Nature of change	Pathway	Produced by/occurs in
Coagulation Formation of fibrin (third stage)	Hypofibrinogenemia	Depression of synthesis in liver	Primary afibrinogenemia Hepatotoxins Hepatic anoxia Severe protein deprivation	Hyperfibrinogenemia	Increased synthesis in liver	Acute infections, rheumatic fever, pregnancy High-protein diet
	Fibrinogenolysis	Activation of plasminogen	Stress, tissue damage, anaphylaxis	Fibrin embolism	Thromboplastin entering circulation	Eclampsia
	Defibrination	Large amounts of tissue thromboplastin entering circulation	Tissue damage, abruptio placentae, eclampsia			
Formation of thrombin (second stage) Prothrombin (II) Accelerator globulin (V) Proconvertin (VII)	Low plasma levels due to specific failure of formation	Primary Depressed liver function Lack of vitamin K	Infancy, congenital deficiencies of II, V, VII, anoxia, laparotomy, general anesthetics, obstructive jaundice, sprue, malabsorption syndrome, antibiotics in bowel	Increased plasma accelerator globulin	?	Abdominal and pelvic surgery, xanthine drugs, etc
		Presence of prothrombopenic drugs in liver	Bishydroxycoumarin, Danilone, Tromexan			
Thromboplastin (III)	Decrease in tissue thromboplastin	Not known	Not known	Increased amounts of tissue thromboplastin entering circulation	Shifts in blood volume Tissue damage	Digitalis Diuretics Trauma, surgical operations
Ca (IV)	Decreased Ca^{++}, significant only when there is also lowering of II, V, VII, X	Depression of parathyroid	Tetany			
Anticoagulants	Heparinemia	Release by mast cells	Anaphylaxis Essential heparinemia (very rare)	Not known	Not known	Not known
	Other	Antibodies to specific coagulation factors	Hemophilia after extensive transfusions			

Continued on Page 487

TABLE II (*Continued*)

Factors Decreasing and Increasing Hemostatic Mechanisms

Hemostatic mechanism affected	Decreasing factors			Increasing factors		
	Nature of change	Pathway	Produced by/occurs in	Nature of change	Pathway	Produced by/occurs in
Formation of plasma thromboplastin (third) stage)	Low plasma levels due to specific failure of formation			Not known	Not known Thrombosis can occur in absence of VIII, IX, X	Not known
Antihemophilic globulin (VIII)		Congenital	Hemophilia A			
Christmas factor (IX)		Congenital	Hemophilia B			
Stuart-Prower factor (X)		Congenital liver disease prothrombopenic drugs	Stuart-Prower syndrome Bishydroxycoumarin, etc.			Increased in stress
Hageman phenomenon (?)		Congenital	Absence does not cause bleeding	?	? Appears to be the essential component for thrombosis	?
Platelets	Thrombocytopenia	Destruction of platelets and depression of megakaryocytes	Essential thrombocytopenia, intravenous therapy, neoplasms Radiation (P^{32}, radium, atomic bomb, etc.)	Thrombocytosis	Increased release of platelets by bone marrow	Adrenaline
		Primary and secondary	Industrial solvents		Increased rate of formation of platelets	After surgical operations (peak on tenth day)
		Toxic Allergic-platelet agglutinins	Multiple blood transfusions, drugs (Sedormid, quinidine, antibiotics, etc.)			
	Thrombasthenia	Idiopathic nonthrombocytopenic purpura	Congenital	Thrombophilia	Increased platelet stickiness	Postoperative (younger platelets) (in circulation)
		Coating of platelets Removal of platelet serotonin	Some dextrans Reserpine			Thrombotic thrombocytopenia

Continued on Page 488

TABLE II (*Continued*)

Factors Decreasing and Increasing Hemostatic Mechanisms

Hemostatic mechanism affected	Decreasing factors			Increasing factors		
	Nature of change	Pathway	Produced by/occurs in	Nature of change	Pathway	Produced by/occurs in
Blood vessels	Decreased resistance to pressure differential (increased fragility)	Discharge of adrenaline	Pain, stress	Damaged endothelium	Trauma Infection Capillary anoxia	Bacterial endocarditis
		Imbalance of adrenal corticosteroids	Physical stress Psychic trauma	Increased resistance to pressure differential (decreased fragility)		Stress Anesthesia (hypoxia, hypercapnea)
		Changes in estrogens	Menstruation			
		Change in cement substance	Deficiency of vitamins C and P			
	Increased permeability	Histamine Serotonin	Anaphylaxis			
		Capillary anoxia Antibodies to endothelium	Arthus reaction	Vasoconstrictor response		Vasopressin Adrenalone Ephedrine
	Loss of vasoconstrictor response	Block of vasoconstrictor impulses	Sympathectomy Sympatholytic agents (ergotamine, 883F, etc.)		Liberation of adrenaline and conversion to adrenochrome	Stimulation of sympathetic, convulsions, anesthetics, injection of adrenaline, sympathomimetic amines
Blood flow	Increased blood pressure	?	Essential hypertension	Hypotension	Vasodilation	Shock
		Discharge or injection of adrenaline	Anger, fear, stress	Stasis	Decreased venous return	Bed rest
		Sympathetic discharge			Local interference with circulation	Tight bandages, edge of chair (on long-distance flights, etc.)
	Increased flow	Increased vasomotor tone Local vasodilation	Local heating, etc. Arteriosclerosis			
		Decreased elasticity of arteries				

Coagulation factors are given in Roman numerals according to the recommendation of the International Committee on Nomenclature of Blood Coagulation Factors.[8] The synonyms shown for these factors are used without any prejudice or implication of priority or mode of action.

It is evident from table II that a given physiological or pathological condition may affect hemostasis at different levels and even in opposing senses. For example, general surgery with anesthesia will have multiple effects. In general, the liver damage produced by anoxia, etc., tends to increase the danger of hemorrhage, and this is further increased by the effects of stress from the preoperative preparation and the operative procedure. The possibility of reactions to transfusions and to drugs increases the possibility of hemorrhage. On the other hand, shifts of blood volume, tissue damage, prolonged depression of the cardiovascular system, and stasis all tend to favor thrombosis. Postoperatively, the thrombocytosis and accompanying thrombophilia increase the thrombotic tendency.

It can also be seen in table II that adrenaline promotes hemostasis by its vasoconstrictor action, yet promotes hemorrhage by its vasopressor activity and as a stress agent, and finally promotes thrombosis by causing thrombocytosis, hyperprothrombinemia, and increased thromboplastin. The nature of adrenaline's action, then, will be a sum of positive and negative effects, and the direction of its action will depend markedly on the concentration in the circulation.

Hemostasis is a remarkably effective process. It is effective because it involves not one but three mechanisms and these are so effective that any one mechanism can be missing without hemorrhage. Spontaneous hemorrhage occurs when there is a defect or damage to several mechanisms simultaneously. This is equally true of the opposite situation, thrombosis. Blood flow is very significant because it modifies these mechanisms. The need for assessing combinations of factors means that focusing attention on one mechanism will fail to explain the occurrence of hemorrhage (or thrombosis), since what appears to be the same situation causes hemorrhage (or thrombosis) in some patients but not in others.

This phenomenon makes difficult the development of any single test for evaluating the possible prognosis for either hemorrhage or thrombosis in the individual patient. However, neither of these deleterious developments occurs without some warning. If all who are involved in patient care are alert to the importance of traces of bleeding, unexplained rise in body temperature, examination of superficial vessels for thrombi, and general evaluation and support of adequate blood flow to the extremities, pelvis, abdominal, and thoracic regions, it can be confidently expected that the incidence of severe complications from both hemorrhage and thrombosis will be reduced. In particular, with the extensive use of anticoagulant therapy today, it is useful to remember that hemorrhage is not simply the natural result of the use of anticoagulants but is a warning sign of a change from the normal, requiring evaluation of the new pathological factor.

SUMMARY

Hemostatic effectiveness varies with changes in the blood that alter speed of formation and strength of the fibrin clot, changes in platelets to affect formation of the *clou hémostatique*, changes in the reaction and integrity of the vascular wall, and changes in blood flow. Changes in the simple clinical tests of clotting time, bleeding time, capillary fragility, etc., and the site of the bleeding reflect the hemostatic mechanism affected, but serious spontaneous hemorrhage does not occur even in the

absence of one of the hemostatic mechanisms. Instead, it requires simultaneous derangement of several mechanisms (multiple causation of hemorrhage). Similarly thrombosis requires simultaneous changes in several mechanisms in the reverse direction. Stress, liver damage, and allergic reactions due to drugs and transfusions increase the possibility of hemorrhage due respectively to reduction in vascular integrity, in coagulation factors, and in platelets. Shifts of blood volume and tissue damage, prolonged depression of the cardiovascular system, and operative surgery increase the possibility of thrombosis due to entry of thromboplastin in the circulation, stasis, and thrombocytosis.

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Course in Rehabilitation Care of the Chronically Ill Patient

A one-week course for physicians, devoted to the rehabilitation care of the chronically ill patient, will be held Nov. 14–18, 1960, under the auspices of the Department of Physical Medicine and Rehabilitation, New York Medical College–Metropolitan Hospital Center. The course will offer a review of the principles and techniques in the medical care of the chronically ill to meet the needs of the clinician, medical administrator, and public health physician. Course content will include: physiology and pathology of chronic diseases, nutrition and dental care, management of bedridden and incontinent patients, home care programming, community needs and resources, public health aspects, self-care activities, prosthetic devices, and psychological and social aspects.

The tuition fee is $150.00. Traineeships for tuition, maintenance, and travel are available through funds provided by the U. S. Office of Vocational Rehabilitation. Applications for the course and traineeships can be obtained directly from Dr. Jerome S. Tobis, Chairman, Department of Physical Medicine and Rehabilitation, New York Medical College, 1 East 105th Street, New York City 29.

Disorders of the Hemostatic Mechanism

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Blood is the circulating internal fluid environment acquired by man during his evolutionary development. This vital liquid is contained by a rather delicate system of vessels. To protect against the escape of blood in the event of injury, there evolved a mechanism of hemostasis, whereby acquired imperfections in the walls of the container system could be sealed. During hemostasis, the physical state of the blood is changed from that of a liquid to that of a gel. Gelation, or coagulation, is controlled by a delicately balanced system of coagulant and anticoagulant forces. When the system is operating at optimal effectiveness, vascular leaks are stanched, but spread of the coagulating forces beyond the local site of bleeding is prevented (hemostatic equilibrium). Should the coagulant forces be defective, there may be excessive hemorrhage; should the mechanisms that control the extent of coagulation fail, deleterious thrombosis may occur.

Obviously, the balance between the antagonistic reactions of the hemostatic mechanism must be shifted from time to time to accommodate demands. In general, the reactions that determine the hemostatic equilibrium can be grouped into those of the vascular wall, the cellular components of blood, and the plasma factors that bring about the production of fibrin. These three groups of reactions have been recognized for many years as playing significant roles in determining the state of balance of the hemostatic mechanism. As is true in most biological systems, there is considerable overlap in the component reactions. Nevertheless, a rational approach to understanding hemorrhagic and thrombotic states is provided when these disorders are viewed as pathological variants of the three basic hemostatic reactions.

VASCULAR REACTIONS

The condition of the vessel wall is of primary importance in the genesis of either hemorrhage or thrombosis. Every hemorrhage results from a break at some point in the vascular system to permit the escape of blood. Certain states, such as congenital saccular aneurysms,[1] polyarteritis nodosa,[2] and possibly scurvy,[3] are associated with sufficient weakness of the vessel walls that rupture and hemorrhages are common sequelae. Conversely, a wide variety of injuries, such as infections or trauma, may produce defects in the intimal lining, which can initiate thrombus formation. It has long been felt that extrahemic "thromboplastic" substances are released from damaged vessels and from neighboring tissues to trigger the fibrin-

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forming mechanism. Although this is an old concept, there is little direct evidence that such a mechanism is of great importance. More fundamental and provocative is the evidence presented that electrical forces may play a role in attracting the components of a thrombus to a site of intimal damage.[4] Normally the intima possesses a negative electrical potential with respect to its adventitia. Such a force would tend to repel the negatively charged cells and proteins of the blood stream. When the vessel is damaged, a positive intimal charge develops instead. Experimentally this positive charge has been shown to be capable of producing local thrombus formation, even to the point of occlusive thrombosis.[5]

Theoretically, contraction of the walls of blood vessels could play an effective role in hemostasis. Certain workers have observed apparent contraction of vessels after injury,[6] but the significance of vascular contraction in hemostasis is uncertain.

CELLULAR REACTIONS

When the need for hemostasis is created through damage to the vascular system, one of the earliest and most dramatic responses is the adherence of blood platelets to the site of injury.[7] This response appears to be related to an increased "stickiness" of the cement between the endothelial cells. The platelets attach to the cement lines and form the primary layer of a thrombus. Agglutination progresses so that other platelets stick to this primary layer, eventually forming a white thrombus of sufficient size to be a fairly effective seal of the vascular defect.[8] Exactly how such agglutination of these small cellular particles is effected is not yet clear. Experimental studies by some workers would indicate that thrombin can agglutinate platelets.[9] In addition, a thrombocyte agglutinating factor has been demonstrated in canine plasma,[10] which, in the presence of appropriate cations,[11] can cause rapid and grossly visible clumping of platelets. Obviously, platelet agglutination will be ineffective as a hemostatic mechanism if there is a deficiency either in platelet numbers or their agglutinability. The former is seen in a variety of conditions associated with thrombocytopenia; the latter, in certain obscure thrombocytopathies.[12] On the other hand, this same mechanism of platelet agglutination perhaps is responsible for initiating and perpetuating many larger and occlusive intravascular thrombi that are accompanied by fibrin formation as well. The other cellular components of the blood, leukocytes and erythrocytes, usually play a more passive role in the formation of hemostatic or pathological thrombi and are only incidentally incorporated into intravascular clots. At times (e. g., in sickle cell disease[13]), erythrocyte aggregation appears to predispose to thrombosis.

PLASMA REACTIONS

The third group of reactions concerned with hemostasis are those that lead to fibrin formation. These reactions have been intensively investigated in recent years, largely because of the ease of sampling the circulating blood and because of the newer biochemical methods available for in vitro studies. The newer knowledge can best be understood as simple extensions of the "classical" theory of blood clotting. According to this theory the blood remains fluid within vessels until it comes

into contact with tissue thromboplastin. This thromboplastin, in the presence of calcium ions, converts the plasma prothrombin to thrombin, which in turn acts on fibrinogen to produce a fibrin clot.

This classical explanation of blood clotting, though it has admirably stood the test of time, does not explain why blood clots in the absence of tissue thromboplastin. Furthermore, the blood of a patient with hemophilia (deficiency of antihemophilic factor) will clot normally with hemophilic tissue juices;[14] yet the patient may have severe hemorrhages. Such discrepancies between the postulated clotting mechanism and observed hemorrhagic manifestations have suggested that there might be two clotting systems—one dependent on tissue (extrinsic) thromboplastin and the other on blood (intrinsic) thromboplastin. Both systems have in common the conversion of prothrombin to thrombin and the action of thrombin on fibrinogen to split off terminal amino acids[15] and initiate polymerization of the fibrin monomer into fibrin threads.[16]

Blood thromboplastin is thought by some[17, 18] to be formed by the interaction of factor IX (Christmas factor, plasma thromboplastin component), factor VIII (antihemophilic factor), and platelets in the presence of factor V (accelerator globulin, proaccelerin) and factor X (Stuart-Prower factor). It then converts prothrombin to thrombin in the same way that tissue thromboplastin does.

Isolated deficiencies of each of the various clotting factors are known to occur. The resulting hemorrhagic diseases vary in severity depending on which factor is deficient and whether the deficiency is complete or partial. Combined deficiencies are produced therapeutically by the use of such anticoagulants as bishydroxycoumarin, which lowers the plasma concentration of prothrombin,[19] factor VII,[19] factor IX,[20] and factor X.[18] In addition, clotting factors may be rendered ineffectual by the occasional development of circulating anticoagulants.[21]

Deviations toward thrombosis also occur in the usually balanced fibrin-forming reactions. That such deviations occur is obvious from the frequent observation of fibrin thrombi in the blood vessels of patients. However, the actual demonstration of "hypercoagulability" of blood is difficult by the methods currently available, although many claims for such an accomplishment have been made.[22] Much work remains to be done on this important problem.

THROMBOHEMORRHAGIC DYSFUNCTIONS

The preceding principles not only serve to explain the occurrence in patients of thrombotic or hemorrhagic imbalance in the clotting system but also offer an explanation for the seemingly paradoxical "thrombosing bleeders." One encounters both thrombotic and hemorrhagic tendencies in polycythemia vera,[23] leukemia,[24] thrombotic thrombocytopenia purpura,[25] purpura fulminans complicating scarlet fever,[26] cold injury,[27] transfusion reactions,[28] lupus erythematosus,[29] and some forms of neoplasia.[22] Clinical, autopsy, and experimental observations have been made that suggest that the basic pathological process is an acceleration of the clotting mechanism within the circulating blood. Sometimes intravascular thrombi form; at other times fibrinolysin and other lytic enzymes are activated and protect the body

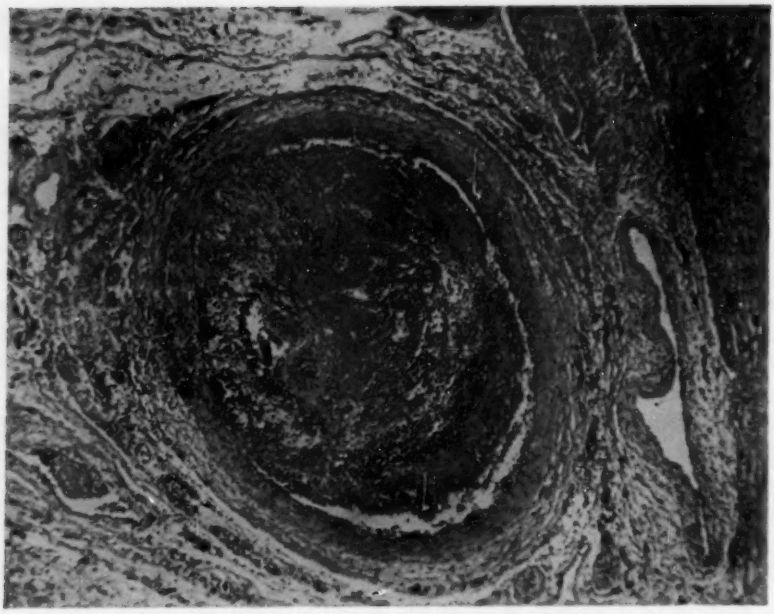

FIG. 1. Thrombosis of coronary artery of a 4-day-old infant.

from the actual deposition of fibrin in the vascular lumina. In either event, however, certain clotting factors are diminished in concentration (e. g., platelets, fibrinogen, antihemophilic factor) and hemorrhagic states are thereby established. The exact mechanism for the loss of the factors is not yet clear. They may be simply dissipated as consumable reactants or be secondarily destroyed by enzymes that become activated by the clotting process.[30]

It is possible to reproduce the proposed sequence of events by injecting tissue extracts into experimental animals.[31] Likewise, many adult diseases, most notably the hypofibrinogenemic complications of pregnancy, are thought to be caused by the escape of tissue thromboplastic substances into the blood stream.[32] It is wholly possible that such a mechanism might operate in infants as well. This was suggested by a case recently observed in our hospital* of a 4-day-old child with pulmonary and coronary thrombosis (fig. 1) and massive myocardial infarction. The thrombi appeared to be of an age that would be consistent with formation at or shortly after birth. No morphological abnormalities were demonstrated in the vascular walls. Considerable damage to the brain had occurred during attempted delivery from an occiput posterior presentation. It was thought likely that this could have resulted in an outpouring of brain thromboplastin into the circulating blood with the consequent production of the fibrin thrombi.

* The post-mortem examination was performed by Dr. James G. Todd, Jr.

CONCLUSION

Modern concepts of the basic mechanisms of hemostasis lead to an understanding of the widely divergent clinical disorders of hemorrhage and thrombosis. The pathogenesis of these diseases can best be appreciated when they are viewed as the result of imbalances in an intricately balanced physiological response to injury. Hemorrhage occupies a position at one end of the spectrum, thrombosis at the other. Their concomitant occurrence in "thrombosing bleeders" especially emphasizes the close interrelationship.

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Diagnostic Procedures in Hemorrhagic Diseases of Children

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The informed physician is aware that the era when tests of bleeding time and clotting time were done preoperatively to "rule out" a coagulation defect has passed. He knows the danger and frustration in proceeding with surgery in a child who apparently is an "easy bleeder." He has probably also experienced the frustration of trying to read the latest literature about coagulation since comprehension of much of it requires an impressive vocabulary of synonyms. Simplification of the coagulation process is problematic because of the great gaps in our knowledge concerning it. The scheme shown in table I is not all-inclusive but outlines the steps that may be investigated by available laboratory methods. Anticoagulants will not be discussed because of their rarity in the pediatric age group.

Most of the coagulation problems in children can be categorized, partially at least, before any laboratory procedure is attempted. None of the available tests is a substitute for a complete history and physical examination. Family history and details of previous symptoms are often more informative than reports of previous laboratory tests. The latter may be more distracting than helpful.

The majority of bleeding problems in pediatric patients are either purpura, inherited hemophilia A (antihemophilic globulin deficiency), or hemophilia B (plasma thromboplastin component deficiency, Christmas disease). Purpuric bleeding is superficial (skin) or epithelial (gastrointestinal, urinary, or nervous systems), and preceding trauma is unusual. Hemophilic bleeding involves deeper structures such as the joints or subcutaneous areas, and ecchymoses appear after trauma. Clean venipunctures rarely produce symptoms in the hemophilic patient. In the child with purpura, a shower of petechiae may appear adjacent to the puncture site.

Diagnostic laboratory work-up of hemorrhagic disease in a child requires precise and time-consuming (and, therefore, expensive) procedures, either not done at all or not done well in most routine hospital clinical laboratories. Judgment should be exercised in deciding when and on whom the tests should be done. For example, if a newborn male infant is hemorrhaging from the umbilical stump, it may be more advantageous to study an older symptomatic sibling. If the bleeding newborn infant is premature, has a noncontributory family history, does not respond to intramuscular vitamin K_1 (1 mg.), and has a normal platelet count, treatment with fresh platelet-rich plasma (whole blood if hematocrit is low) may be more important than traumatic venipunctures. Inadequate or contaminated blood specimens are useless. A poorly controlled coagulation test does not aid in diagnosis or therapy.

Coagulation tests require experience and care to recognize the variability of normal control blood and the significant deviations from normal. The first step in establish-

TABLE I

The Coagulation Process

Stage of coagulation	Known requirements (+ calcium) for normalcy
I. Formation of thromboplastin	Platelets
	Foreign surface
	Antihemophilic globulin
	Hageman factor
	Plasma thromboplastin component
	Stuart-Prower factor
	Plasma thromboplastin antecedent
II. Formation of thrombin	Thromboplastin
	Prothrombin
	Factor V
	Factor VII
	Stuart-Prower factor
III. Formation of fibrin	Thrombin
	Fibrinogen
IV. Clot retraction	Platelets
	Fibrin

ing any diagnostic test is the determination of an adequate range of normal for the individual laboratory. Variability in any reagents used or prepared by the laboratory requires constant attention. Glassware, plastic tubes, etc., used for coagulation studies should not be used for other laboratory procedures. All used tubes should be kept immersed in mild bicarbonate solution or water until thoroughly cleansed. Dried plasma clots and proteins may be difficult to remove from glass test tubes and may interfere with reproducibility of clotting times.

Clotting time or the time of appearance of fibrin is the universal end point of coagulation procedures from the simplest to the most complicated. Any measure that increases the visibility of fibrin formation increases the reproducibility of clotting times. Stopwatches and an incubator or well for temperature control are essential. Most tests are performed at a temperature of 37 C. The following listing begins with the simplest tests and proceeds to the more specialized ones. All give some information, although specificity is limited in most.

PLATELET COUNT

The Rees-Ecker and phase contrast methods are the most reliable.[1] Normals for children are 220,000 to 360,000 platelets/cu. mm. of blood. The count may be elevated in the newborn infant, post splenectomy, in severe anemia, infections, or chronic myelocytic leukemia. It may be decreased after massive replacement transfusions with stored blood (erythroblastosis, extracorporeal circulation for cardiac surgery), in purpuric diseases, hypersplenism, and any pathological or therapeutic process causing bone marrow replacement or depression. A peripheral blood smear may show evidence of leukemia or other neoplastic disease. Thrombocytopenia is generally an indication for diagnostic bone marrow aspiration.

TOURNIQUET TEST

A blood pressure cuff is inflated on the patient's arm and maintained at a pressure midway between diastolic and systolic for five minutes. Normal children may show scattered petechiae on the arm when the cuff is removed. If the test is positive, the cuff should be removed as soon as a shower of petechiae appears, since evidence of capillary fragility is all the information that is sought. The test is correlated with the bleeding time and is often more conclusive.

BLEEDING TIME

Capillary bleeding time is frequently an unreliable procedure in infants and children. Even with skill and long experience, repeated determinations may be required to establish the validity of the bleeding time. Different methods of performing the test have less variability than the physical state of the infant and the technique at the time the test is done. It is irrelevant to discuss the comparative results of bleeding times from ear puncture, finger puncture, toe puncture (Duke[2]), forearm puncture,[3] etc., not observed by the physician trying to evaluate the results. The uniformity of the lancet puncture and the pressure reading of a manometer cuff are minute variables compared to the physiological state of the child when a bleeding time is done. If the child is old enough and is cooperative, the Duke method done in duplicate may be reliably compared to adult control values. If he is crying, struggling, febrile, cold, or in a state of shock, results are not informative.

Since skin thickness and subcutaneous fat vary tremendously in young children, a given puncture depth does not ensure reliability. Reproducible bleeding times (Duke method) can be obtained in infants by the patient and skilled physician who takes the time to pacify the child. In very young infants, we choose to determine bleeding times in both great toes. After the puncture, the infant's foot is allowed freedom until the reaction to pain subsides (30 to 60 seconds). He is then offered a pacifier while the observer's hand holds the test foot firmly but gently to blot the puncture site every 15 seconds for bleeding time determination. Control values range from two to six minutes and there is rarely a variation of more than 45 seconds in duplicate determinations. The Ivy method[3] is useful only in the older, cooperative child.

The most common cause of a prolonged bleeding time in children is thrombocytopenia. The time is also increased in patients with or without a demonstrable microscopic capillary defect associated with decreased antihemophilic globulin ("pseudohemophilia," "vascular hemophilia").

CLOT RETRACTION AND LYSIS

If sufficient blood is available, 5 ml. is placed in a centrifuge tube and a wire hook stuck in a cork is suspended in the blood.[4] The stoppered tube is incubated at 37 C. for one hour. The clot is removed and the volume of serum recorded. A hematocrit is done. The clot volume minus the hematocrit is the fluid volume of the clot. The percentage of fluid in the clot is the most accurate indicator of clot retraction. Visual estimates of clot retraction are adequate only if the child's hematocrit is normal.

The test is abnormal with thrombocytopenia or with the rare purpura associated with a deficiency of the platelet clot retraction factor (Glanzmann's disease).

Clot lysis may be observed by watching a well-formed clot return to a fluid state in a 24-hour period.

CLOTTING TIME

Normal clotting times vary with the method used and the individual's use of the method. The procedure most commonly done is a modification of the Lee-White test. Normal control values are necessary for evaluation of the patient's clotting time. A venous puncture is done with a sharp needle. The first few drops of blood are discarded and a clean, dry syringe is used to withdraw 3 ml. of blood. A stopwatch is started at this time. One ml. of blood is gently placed into each of three standard, clean, dry test tubes, kept at 37 C. After one minute, each tube is tilted every 30 seconds until inversion of the tube without spilling of blood is accomplished. Clotting time recorded is an average of the three tubes. Normal clotting times are longer if: done at temperatures lower than 37 C.; tilting of successive tubes is begun only after clotting of the first tube; tilting is done at less than 30-second intervals; wetting agents have adhered to the tubes; or siliconized syringes or tubes are used. They may be shortened by: unsatisfactory venipuncture (needle dull or too small, hematomas, extraneous material on skin surface, etc.); dirty needles, syringes, or tubes; squirting of blood from syringe to tubes with foaming; temperatures greater than 37 C.; vigorous tilting or shaking of tubes.

Clotting time may be abnormally increased with deficiencies in any of the aforementioned three stages of coagulation (table I). Prolongation is a gross, nonspecific indication that a defect exists. A normal clotting time, on the other hand, is no assurance that the clotting mechanism is normal.

PLASMA RECALCIFICATION TIME

When 0.1 ml. of $M/40$ calcium chloride is added to a tube containing 0.1 ml. of normal plasma and 0.1 ml. of physiological saline incubated at 37 C., a visible fibrin clot forms in 90 to 220 seconds. Deviations from normal are seen with severe deficiencies in coagulation factors. The variabilities noted previously are also pertinent to this test. The concentration of citrate in the plasma is an additional consideration.

PROTHROMBIN TIME

The one-stage prothrombin time measures the last two phases of coagulation since a prepared tissue extract (human, rabbit, bovine) supplies thromboplastin for the reaction. Citrate plasma and tissue extract, 0.1 ml. each, are placed in a test tube at 37 C. After 15 seconds' incubation, 0.1 ml. of $M/40$ calcium chloride is added and a clotting time is done. The test is performed in duplicate with both normal control and patient's plasma. Normal prothrombin times vary (10 to 14 seconds) with the reagent used, but are constant for a given batch of extract.

The test is normal in most patients with an inherited coagulation deficit, e. g.,

hemophilia, Christmas disease, or plasma thromboplastin antecedent deficiency. It may be abnormal when there is a circulating anticoagulant or when any factors involved in stage II and stage III of the clotting scheme are deficient. The prolonged one-stage prothrombin time in the normal newborn infant is rarely of sufficient magnitude to produce hemorrhagic symptoms. It has been estimated that any one or several of the factors mentioned is less than 30 per cent of normal when the prothrombin time is significantly prolonged. In the newborn infant, this may occur due to a deficiency of vitamin K. In the older child, hepatic disease or sterilization of the gastrointestinal tract with antibiotics and intravenous feeding may cause a similar deficiency. Congenital lack of prothrombin, fibrinogen, factor V, VII, or Stuart-Prower occurs but is rare. The one-stage prothrombin time has been used to regulate anticoagulant therapy. Such therapy is rarely indicated in pediatric patients and is incompletely assessed by this test.

PROTHROMBIN CONSUMPTION TEST

Coagulation is a dynamic physiological mechanism that neither begins nor ends with the production of a visible fibrin clot. After a visible blood clot has formed, prothrombin in the serum is utilized as clotting progresses and more thrombin is produced. The constituents of blood necessary for this continuing utilization or "consumption" are chiefly those involved in the production of blood thromboplastin.

After the Lee-White clotting time has been performed, the tubes are incubated at 37 C. for exactly one hour after the clot has formed; 0.1 ml. of sodium citrate (3.8 per cent solution) is added to each tube to halt the reaction. The clots are rimmed with an applicator stick, the tubes are centrifuged at 2000 rpm for five minutes, and the serum from the tubes is pooled. This serum may then be frozen until a two-stage prothrombin test or "specific" prothrombin assay is performed.[6] Normal blood shows a definite decrease in prothrombin in serum after one hour of incubation. In patients with severe hemophilia or thrombocytopenia, serum prothrombin levels may approximate those of plasma.

A normal prothrombin consumption test may be obtained in patients with hemophilia or thrombocytopenia. It is usually abnormal if the deficiency is severe. The test is of limited value as a diagnostic tool and is of even less help as an indicator of possible postoperative hemorrhage in a hemophilic patient. It is, however, a more precise screening method for congenital coagulation defects than is the venous clotting time.

THROMBOPLASTIN GENERATION TEST[7]

The most common inherited or congenital clotting abnormalities are due to a deficit of one of the factors necessary for stage I of coagulation: the formation ("generation") of thromboplastin. These factors may be divided into those that are not absorbed from oxalate plasma by barium sulfate (antihemophilic globulin, ± plasma thromboplastin antecedent) and those that remain in serum after clotting has occurred (plasma thromboplastin component, Stuart-Prower factor, plasma thromboplastin antecedent). Platelets and calcium are also necessary for thrombo-

plastin formation. If one takes venous blood and separates it into three parts—barium sulfate–absorbed oxalate plasma, serum, and platelet suspension—and incubates aliquots of these three reagents with calcium chloride, a potent thromboplastin is formed in vivo. Aliquots of this incubation mixture, when added with calcium chloride to a substrate plasma (supplying prothrombin and fibrinogen), produce a visible minimum fibrin clotting time of 9 or 10 seconds in normal blood. If any of the factors essential for the first phase of coagulation are significantly decreased, minimum clotting times are greatly prolonged. By substituting the patient's platelets, barium sulfate–absorbed plasma, or serum individually in an otherwise normal system, his defect can be categorized. Conversely normal platelets, absorbed plasma, or serum may be substituted in the test of the patient's blood to demonstrate normalization. If plasma or serum from known hemophilic patients is available, confirmatory evidence of antihemophilic globulin or plasma thromboplastin component deficiency may be obtained.

The thromboplastin generation test is a most useful diagnostic test for inherited clotting disorders, since most of these involve this stage of coagulation. Sometimes the test is impractical. In the newborn infant, the amount of blood required is a real consideration and has led to the frequent use of a platelet substitute[8] when the quantity is limited. The thromboplastin generation test is of little assistance in the management of surgery or massive hemorrhage from trauma in a hemophilic patient. Frequent determinations are impractical and the test is relatively insensitive to pertinent changes in the lower range of antihemophilic globulin or plasma thromboplastin component levels. Venous clotting time and prothrombin consumption are even more unreliable if not interpreted wisely. For example, there may be no need for specific assay of antihemophilic globulin or plasma thromboplastin component if venous clotting time or prothrombin consumption remains abnormal despite therapy. However, if the gross clotting time is normal, specific assays are the most reliable therapeutic guide.

SPECIFIC ASSAYS

Reproducible methods have been developed for the assay of prothrombin,[6] antihemophilic globulin,[10] plasma thromboplastin component,[11] Stuart-Prower factor,[12] fibrinogen,[7] factors V and VII.[9] Of these, fibrinogen and perhaps prothrombin assays are the most frequently performed in clinical laboratories. The other determinations are generally done only in special coagulation laboratories and are essential to the best management of severe and uncontrolled hemorrhage in a child with an inherited coagulation disorder.

By means of specific assays, one obtains plasmas in which a single defect may be demonstrated. Such plasmas are useful in simpler diagnostic tests on unknown patients. For example, if a patient's recalcification time or thromboplastin generation test are completely corrected by plasma known to be deficient in antihemophilic globulin, the patient has a defect other than that found in classical hemophilia. Conversely, if the patient's plasma is not corrected by the antihemophilic globulin–deficient plasma and his bleeding time and the platelets are normal, it can be assumed he has classical hemophilia.

Anticoagulants to all of the known coagulation factors have been reported and their presence may account for abnormalities in any of the afore-mentioned clotting tests. They are extremely rare in children. As mentioned previously, none of the laboratory tests are more important than efforts to obtain a complete history.

Occasionally a child is seen whose history arouses suspicion of the existence of a coagulation defect but all laboratory tests are normal and no microscopic capillary defect is demonstrable. It is probable that the patient who has required transfusion because of hemorrhage from the umbilical stump, circumcision, tooth extraction, or tonsillectomy will bleed again when surgery is undertaken regardless of the results of coagulation tests. Fresh platelet-rich whole blood (or plasma as needed), drawn into plastic or siliconized containers, supplies all known coagulation factors and should be available if surgery is anticipated.

The high incidence of recurrent epistaxis in some children, particularly those with a known allergy, has led to repeated investigation of the coagulation factors in this group. No demonstrable defect has been found and problems with postoperative or traumatic bleeding have not occurred in these children. Local therapy offers some benefit, but epistaxes frequently continue until puberty.

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Management of Blood Clotting Defects in Children

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It is fairly easy to give an appreciation of the difficulties of the problem of blood clotting defects in children; it is much more difficult to give a precise final account of the methods of management of these disorders. That will be possible only when large quantities of concentrated preparations of human antihemophilic globulin (factor VIII) and of Christmas factor (plasma thromboplastin component, factor IX) become available.

THE EXTENT AND NATURE OF THE THERAPEUTIC PROBLEM

During the last 10 to 15 years there has been a tremendous surge of interest in the genetically determined hemorrhagic diseases. It should be appreciated, however, that even the commonest of these diseases are rarities. The relative incidence of the various defects varies slightly in different parts of the world. In the three million population of western Scotland, there is one constitutional "bleeder"/20,000 of the population. One sixth of the hemophilic population suffer from Christmas disease, the remainder from hemophilia. The only other cases of genetic coagulation anomalies occurring here are antihemophilic globulin deficiencies in pseudohemophilia or von Willebrand's disease, the condition characterized by a prolonged bleeding time.

Of the patients with either hemophilia or Christmas disease, about one half are less than 12 years old.

These incidences are mentioned in the hope that they may bring into the correct perspective the therapeutic problem involved, namely, deficiencies of antihemophilic globulin and the Christmas factor. It is appreciated, as mentioned, that this is not necessarily true in all areas of the world, but it is nevertheless likely to give an overall index of the requirement for replacement therapy. In New York, for instance, there appear to be fairly numerous cases of plasma thromboplastin antecedent deficiency, but there are none in this region; in Switzerland, the relative incidence of Christmas disease is higher than that of hemophilia. The total world incidence of genetic deficiencies of factor V, factor VII, and Stuart-Prower factor (factor X) must be very small in comparison with the occurrence of deficiencies of antihemophilic globulin or the Christmas factor. Despite the recent appreciation of the different entities within the group of genetically determined hemorrhagic diseases, the most common condition is still hemophilia—deficiency of antihemophilic globulin.

Despite the fact that these diseases occur at a rate of only 1 in 20,000 of our local population, they give rise to a problem that is out of proportion to their incidence. The severely affected hemophilic child may spend half of his childhood in the hospital with one incident or another. From a survey of the records of the children's

hospital in this city, it was found that the severely affected child will be admitted about three or four times in a year, while the child with a mild or moderate defect will only require hospitalization once in every two or three years.

These diseases, of course, occur in an extraordinary range of severity. At the severe end of the scale is the child who has a greatly prolonged whole blood clotting time and no measurable antihemophilic globulin (or Christmas factor). He will be hospitalized with numerous incidents throughout his childhood. He will suffer not only the abnormal hemorrhage that follows minor injury but also incidents of apparently spontaneous bleeding; he will have frequent recurrence of hemarthrosis. He will have a life of chronic invalidism during his childhood and indeed for the rest of his life. At the other end of the scale is the child with the mildest defect; he will have a normal whole blood clotting time and a readily measurable amount of antihemophilic globulin or Christmas factor (up to 20 to 30 per cent). This type of abnormality may go completely unsuspected during childhood, the condition becoming apparent only at the first extractions of permanent teeth, possibly in the teens or later. The child with this grade of defect leads a normal life unless his hemostatic mechanism is put under some excessive strain, such as occurs with an operative procedure like dental extraction or tonsillectomy. When this child has a hemorrhagic emergency, the principles of management are essentially the same as those for the severe case. The problem is slightly easier insofar as the patient is already at some advantage over the severe case, having an appreciable initial level of antihemophilic globulin or Christmas factor.

If we consider these two deficiencies together, about half the children are severely affected and the other half are only mildly or moderately affected. Both hemophilia and Christmas disease occur in the same grades of severity, but the relative incidence of severe hemophilia among hemophilic persons is greater than that of severe Christmas disease among patients with Christmas factor deficiency.

MANAGEMENT WHEN THE CHILD IS FREE FROM AN ACUTE HEMORRHAGIC INCIDENT: INSTRUCTIONS TO THE PARENTS

It is most important that the physician in charge of the child should gain the confidence and cooperation of the parents and relatives. They must learn, as must the child, to live with the problem. They should be interviewed at intervals and kept abreast of current progress in the management of this disease. It should be made clear that the ultimate goal of present research is the provision of a potent preparation of the missing clotting factor, which could be made available for daily prophylactic administration, in the same way as insulin is provided for the diabetic person.

When the defect is mild, it is important to stress to the parents that this is so and that only the more violent or potentially more dangerous types of activity need be restricted. The use of the term "hemophilia" in describing one of these milder cases tends to make some parents restrict the activities of the child unduly. On the other hand, an explanation of the gravity of the defect should not be withheld from the parents when the child has severe hemophilia or Christmas disease.

In the management of these patients, the motto of "prevention is better than cure" applies with particular emphasis. It is of importance that the parents be aware of the commoner manifestations of the disease. This is important for the parents of those children who have already been diagnosed as suffering from the disease. It is also of value for the parents of children who have not yet been diagnosed as suffering from the disease, but where there is a possibility of the condition in view of our knowledge of the pattern of its inheritance. The features of the disease should be explained in the following terms. Trivial cuts, in childhood particularly of the scalp or the lips, gums, tongue, or face, may bleed for an unduly long time—for hours, days, or weeks; the same prolonged bleeding may follow minor operations such as tooth extraction, tonsillectomy, or circumcision. Sometimes even without any physical injury the child's skin may bruise abnormally easily, and sometimes for no apparent reason there may be bleeding into joints with resultant sudden swelling, or there may be bleeding into muscles. It should further be explained that bleeding internally can be at least as serious as obvious external bleeding.

The attendant physician has a responsibility to explain to the parents the genetic implications as regards any future children they may have and the potential hazard of new cases in the succeeding generations. It should be explained that the daughters of an affected man will be transmitters. In the family of a transmitter, there is a 50 per cent chance that the sons will be affected and that the daughters will be transmitters.

A special card should be issued to the parents; this will give details of the diagnosis and of the blood group, with data on any abnormal red cell antibodies known to be present. It should also give any other information considered relevant; for example, the presence of an anti-antihemophilic globulin inhibitor should be noted. It should be explained to the parents that this card should be shown to any dentist or physician they attend who is unfamiliar with the case. The parents sometimes decide for themselves that the symptoms of an illness are unrelated to the hemophilia and may fail to reveal this vital information.

The ability of the parents to deal with a specific incident will improve with experience in dealing with the condition. A mother of an affected child may already have had such experience from the care of her own brother affected with this disease. As their experience grows they come to appreciate which incidents they can manage at home and which incidents require hospital admission. If the mother is experienced in nursing the hemophilic child, it is possible that such children, even with a severe defect, may reach the age of 10 or 11 years without once having been in the hospital. It is indeed occasionally true that the intelligent parents of a hemophilic child have better judgment in the management of their child's hemorrhagic incident than the attendant doctor has. This is understandable with such a rare disease.

Further instruction should be given to the parents along the following lines. Sensible precautions must be taken to prevent injury, but inevitably the hemophilic child will have at least some share of the usual minor injuries of childhood. The wound should be covered with an absorbent dressing, such as gauze or cotton wool, and firmly bandaged, but not so tightly as to constrict the blood supply. When the cut is on the lip or the tongue, this may have to be held digitally by the mother,

if need be for long periods of time. This is the type of circumstance where a patient, sensible parent can contribute so much to the care of a hemophilic child. Cold water or ice compresses may well be helpful in reducing hemorrhage.

The care of the teeth is another subject that must receive particular attention during the time when the child is free from a major hemorrhagic incident. Regular cleaning and, in particular, regular dental supervision are essential. It should be explained to the parents that the deciduous teeth can decay very easily and that young children should be examined by a dentist every three to four months so that these teeth can be preserved until they fall out naturally. It should be explained that there is much less bleeding when these teeth shed naturally, as compared with extraction before this time. It is of at least equal importance to see that the permanent teeth are well preserved by conservative means. The appalling possible subsequent difficulty of extraction of a large number of the permanent teeth from the hemophilic person should be explained to the parents. It might even be advisable to fluorinate the drinking water of the hemophilic person.

The parents should be told that, if the hemophilic child becomes anemic from excessive bleeding, administration of iron will readily build up the lost blood. The resilience of the hemophilic patient in recovery from an incident is very remarkable.

There are, of course, some psychological and personal difficulties to be overcome. It is hard for the child to have to face the fact that he is different from other children and that he cannot be permitted to undertake all their activities. The problem should be explained to him as soon as he can understand the reasons; it should be discussed openly with him and in front of him; he should not be made to feel that it is something mysterious or not to be spoken of. He should be made to see that he is not the only child with a difficulty to meet, and he must be encouraged to take pride in the things he can do.

The education of the hemophilic child is, of course, a major problem. The severely affected child will inevitably have numerous long absences from school. Home tuition is a partial answer to this problem. Another possibility is the residential school for severely handicapped children. Their education is of supreme importance as they are unlikely subsequently to earn their livelihood in other than a sheltered occupation.

MANAGEMENT OF THE INDIVIDUAL INCIDENT

There is seldom any diagnostic difficulty; any illness in a hemophilic child should be suspected as being due to hemorrhage, unless there is very convincing proof to the contrary. For example, a hemophilic child with a suspected appendix abscess usually has an iliopsoas hematoma, which can be identified by the accompanying right femoral nerve lesion.

The most common causes of hospital admission are hemarthrosis, bleeding after tooth extraction, hematomata, bleeding from cuts, particularly of the lips, mouth, tongue, and scalp, gastrointestinal bleeding, and hematuria. It is well for the attendant physician to be aware that the pressure effects of hematomas are often more serious than the external blood loss from prolonged bleeding.

Injection Technique. Meticulous needle technique is essential. Collection of venous

blood or giving an infusion should not be delegated to the most junior member of staff. Because of the major importance of their veins to these patients during their lifetime, all possible effort must be made to avoid "cutting down" and inserting a cannula. Subcutaneous and intramuscular injections should be avoided. When they must be used, they should be given in the upper arm or thigh in such a manner that a crepe bandage can be applied immediately after injection. The bandage should also be applied after venipuncture. When sedation is required, it should be oral meperidine, methadon, or, if need be, morphine.

Replacement Therapy. In regard to specific replacement therapy, there is great difficulty in producing hemostatic levels of antihemophilic globulin or Christmas factor with currently available sources of human antihemophilic globulin or Christmas factor. After administration, to an adult hemophilic patient, by rapid infusion of 1 liter of fresh plasma, an antihemophilic globulin level of 15 to 20 per cent is attained; the half life of this material in vivo is approximately nine hours. This level of antihemophilic globulin is of only moderate hemostatic efficiency, and for complete efficacy, a level of 30 to 40 per cent is necessary. This is a measure of the magnitude of the problem involved.

Thus, the problem is one of supply and demand. Even though the requirement of the adult hemophilic person is obviously greater than that of the child, there is still in the child great difficulty in producing hemostatic levels with available sources of human antihemophilic globulin.

The available sources of human antihemophilic globulin are: bank blood, fresh plasma, fresh plasma maintained frozen from the time of collection, fresh plasma dried immediately after collection and stored, and dried fibrinogen factor, which is rich in antihemophilic globulin. It is extremely difficult to maintain antihemophilic globulin on storage, and the methods just outlined are on occasion disappointing, but they represent the best currently available.

Bank blood must be used immediately after withdrawal. Blood that is 24 to 48 hours old may on occasion have reasonable preservation of antihemophilic globulin, but in the majority of bottles, only trace amounts will be present.

Fresh plasma immediately separated from the red cells will be rich in antihemophilic globulin; the centrifugation and separation of the plasma must be done with minimal delay. If this fresh plasma is maintained frozen, the preservation is much improved over that of bank blood, but it is still very variable. The average bottle at three months will have 50 per cent of its antihemophilic globulin level. The potency of the dried fresh plasma is also variable.

Dried fibrinogen fraction rich in antihemophilic globulin is a most valuable source if sufficient material is available and if special precautions are taken in its preparation.

In a hemorrhagic incident, the immediate natural reaction is to give the specific replacement therapy. This must be weighed against the difficulties of obtaining an adequate level and, once obtained, of maintaining this possibly for days on end. The use of replacement therapy for management has often resulted in the inadequate and unskilled use of replacement antihemophilic globulin to the neglect of simpler measures. It seems simpler, for example, to use 1 pint of fresh frozen plasma in the management of bleeding from a cut lip than to hold this cut by hand for one hour.

After the latter measure, there may well be recurrence of bleeding, but the same is true some hours after the plasma.

I certainly do not wish to dissuade the physician from using replacement therapy, but it must be used with an appreciation of the problem. It should be used with full facilities available for assay of antihemophilic globulin.

The fibrinogen fraction has the advantage of smaller volume. It is surprising, however, how well large volumes of plasma are tolerated by these patients. The following is given as a very general guidance to therapy: adults, 1000 ml. every 9 to 12 hours; children 12 years old, 500 ml. every 9 to 12 hours; children 9 years old, 400 ml. every 9 to 12 hours; children 6 years old, 300 ml. every 9 to 12 hours; children 3 years old, 100 ml. every 9 to 12 hours. The amount of fibrinogen fraction required depends largely on the potency of the yield of antihemophilic globulin. An average dosage scheme would be as follows: adults, 8 Gm. every 9 to 12 hours; children 12 years old, 4 Gm. every 9 to 12 hours; children 9 years old, 3 Gm. every 9 to 12 hours; children 6 years old, 2 Gm. every 9 to 12 hours; children 3 years old, 1 Gm. every 9 to 12 hours.

Very active preparations of antihemophilic globulin are available from animal sources (porcine and bovine).[1–3] Because of the potential antigenic risk, these preparations can be used only once in a 10-day period for one particular life-endangering incident.

The problem in the replacement of Christmas factor is essentially the same as regards attainment and maintenance of levels. The half life in vivo of Christmas factor is similar to that of antihemophilic globulin. Preservation in bank blood and frozen plasma is appreciably better than that of antihemophilic globulin, but they are not completely stable. Bank blood, fresh plasma, and fresh plasma maintained frozen or dried are the only preparations generally available for replacement purposes.

A number of particular problems require special mention simply because of their frequency. Decayed deciduous teeth often cause bleeding from the adjacent gum. Skilled local dental management may obviate extraction. As discussed previously, extraction of deciduous teeth should be avoided; the great importance of conservative dentistry has also been stressed. The management of tooth extraction is one of the major therapeutic problems in hemophilia, but it cannot be described in this brief account; reference should be made to published descriptions.[4, 5]

Recurrent hemarthrosis is a very common problem. There is a good argument in favor of aspiration, but personally I am not prepared to advocate this as a routine measure until human antihemophilic globulin is available in sufficient amounts to produce hemostatic cover. If it is available in sufficient quantity to cover the procedure itself and to maintain hemostatic levels for three to four days thereafter, then aspiration may be considered in selected cases. Nonoperative orthopedic care can, with attention to detail, do much to help prevent or treat knee deformity.

ACKNOWLEDGMENT

I am grateful to Dr. Cairns, Medical Superintendent of the Royal Hospital for Sick Children, Glasgow, Scotland, for information on the admission rates of hemophilic children.

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SURGICAL MOBILIZATION OF THE STAPES. Surgical mobilization of the stapes was attempted in 138 ears of 100 patients between the ages of 50 and 73 years whose hearing had been impaired for from 10 to 50 years (J. Am. Geriat. Soc., April, 1960). There was significant improvement in 54 per cent of the ears after the first operation and in 67 per cent after a second operation. The median improvement was 20 to 25 decibels. Operations performed in several cases of a seemingly "deaf ear" gave results enabling effective use of hearing aids.

ORAL RESUSCITATOR. Mouth-to-mouth breathing without direct contact with the victim is made possible by a new flexible face mask for the victim with an attached tube used by the rescuer (marketed as Venti-Breather by Venti-Breather Products, Washington, D. C.). As the victim's lungs deflate, a one-way valve directs his breath away from the rescuer's mouth.

TREATMENT OF KELOIDS. Success in treating keloids with Grenz radiation was reported at the recent Atlantic Dermatologic Conference held in Baltimore. Results with this low-voltage radiation have been vastly better than with conventional radiation therapy, according to the report. Four patients treated are without symptoms, and in the earliest case, there has been no recurrence of keloids in seven years.

ANTIASTHMATIC. A sustained-action, controlled-release form of oral aminophylline (Dura-Tab S.M. Aminophylline tablets, Wynn) provides freedom from gastric distress; only a fraction of the medication is released in the stomach, with the balance being absorbed over the entire intestinal tract. The drug is indicated in chronic asthma, congestive heart failure, paroxysmal dyspnea, Cheyne-Stokes respiration, angina pectoris, pulmonary edema, and other cardiopulmonary conditions.

LEUKEMIA IMPROVED BY DRUG. Vincaloleukoblastine, an alkaloid derived from the periwinkle plant, caused significant improvement with decrease in spleen size in 21 patients with all types of leukemia, according to a recent report to the American Association for Cancer Research. Administration of single daily intravenous doses of 0.1 to 0.5 mg./Kg. for several days at a time produced remissions lasting only one to six weeks, but when the drug was given intermittently, some patients showed improvement for as long as three months.

TEST FOR LUPUS ERYTHEMATOSUS. A new simple test for diagnosis of disseminated lupus erythematosus consists of adding a drop of the patient's serum to bentonite sensitized by desoxyribonucleic acid (Proc. Soc. Exper. Biol. & Med., March, 1960). If the disease is present, clumping will develop in the mixture in a few minutes. Testing with the new procedure confirmed the diagnosis obtained earlier by the slower, more elaborate lupus cell test in 8 lupus patients. Controls used were 138 serums from normal persons.

FOOT GUARD. A lightweight metal frame is designed to shield the injured forefoot, particularly the toes, in patients convalescing from fractures, dislocations, and other conditions where shoe pressure is contraindicated (marketed as Podo-Shield by Universal Products & Techniques, Beverly Hills, Calif.). The device is easily attached to the cut shoe and can also be used with postsurgical wooden-soled sandals.

NEW PALATE OPERATION. A new surgical technique to close and lengthen a cleft palate in a single, one-hour operation is said to prevent the fuzzy speech patterns that sometimes follow palate operations, according to a report at the recent meeting of the Association of Plastic Surgeons in Milwaukee, Wis. The palate is lengthened by transferring to it a flap of mucous membrane and muscle from the pharnyx; the flap prevents a leakage of air into nasal passages, which causes indistinct speech. The technique has been used on 22 infants.

ANTIBIOTIC SPRAY POWDER. An antibiotic spray powder (Neobacin Spray, Commercial Solvents Corp.), consisting of equal weights of neomycin and bacitracin, was used as an adjunct to the exposure therapy of severe burns in 21 patients (AM&CT 7:291, 1960). The burns were second and third degree in depth and involved 5 to 85 per cent of the body surface. In all cases healing progressed satisfactorily without any evidence of infection, irritation, or allergic reaction. In cases in which skin grafts were necessary, the previous use of the topical medication did not interfere with the "take" of the grafts.

ANTI-POISON IVY. Now available as a foam is an anesthetic-analgesic combination of zirconium oxide, calamine, benzocaine, menthol, and camphor (Rhulifoam, Lederle), to provide cooling relief of minor itching and pain associated with ivy and oak poisoning as well as urticaria, insect bites, and other minor skin irritations. The medication dries promptly, providing a protective film over affected skin.

Decisive Books in Medical Progress

Ralph H. Major, M.D.

DEPARTMENT OF THE HISTORY OF MEDICINE,
UNIVERSITY OF KANSAS SCHOOL OF MEDICINE
KANSAS CITY, KAN.

The history of many sciences is readily traced by a consideration of their outstanding books. Medicine is no exception. In medicine, however, we have such a plethora of books that it is difficult to choose the outstanding works that light the path of medical progress. This plethora dates from the earliest times. When Socrates twitted Euthydemus by remarking, "Of course you who have so many books are going in for being a doctor, there are so many books on medicine, you know," he was referring to the well-known state of affairs in Greece of the age of Pericles. An even more striking example has come down to us from the Antonine age of Imperial Rome when the great Galen remarked, "You are right, my good Bassius, in saying that I should write a little book on my own books."

Yet despite this flood of medical books down through the centuries, when so many works, after riding high on the crest, were then washed away into oblivion, certain great works have survived to immortality. Even the survivors are legion, and probably no two students of the history of medicine would select the same examples as those most worthy of immortality. Nevertheless, just as certain battles have been decisive in the history of the world, so certain books have been decisive in medical thought.

One of the most venerable medical books in existence is the Ebers Papyrus, composed c. 1550 B.C. and translated by Prof. Georg Ebers in 1873. This work, with the Edwin Smith Papyrus, translated by Prof. J. H. Breasted in 1930, gives us a fairly clear picture of Egyptian medicine in the days of the Pharaohs. The Ebers Papyrus considers the heart as the center of the vascular system and describes many diseases, some 30 or 40, of the ancient Egyptians from which modern man suffers. Drugs were administered by mouth, by inhalation, and by local application. Enemas, pills, infusions, electuaries, eye drops, ear drops, gargles, fumigations, mud baths, and sitz baths are mentioned. The author or authors recommend castor oil, podophyllin, and senna as purgatives, turpentine and pomegranate for intestinal worms, and beef liver for night blindness. The Ebers Papyrus describes one of the earliest known contraceptives, acacia tips, which, when moist, liberate lactic acid, a powerful spermicide.

While there may be doubt that the Ebers Papyrus made a deep impression on the course of medicine in the years after its compilation, there is no question regarding the influence of the Hippocratic books. For more than a millennium after the appearance of the Hippocratic books, no physician who wished to be considered learned and wise failed to write a commentary on some work of Hippocrates. The dispute regarding the authenticity of the Hippocratic treatises probably began soon after Hippocrates' death and it has continued unabated. Some critics have described Hippocrates as a simple Greek itinerant surgeon while others have called him a

The Ebers Papyrus.

myth. However, he was no myth, for we have the testimony of Plato, a contemporary, and the veneration not only of his contemporaries but of later intellectuals, such as Aristotle, does not suggest that Hippocrates was a simple itinerant surgeon. Obviously, he could not have written all the works attributed to him. The *Hippocratic Corpus*, as Jones suggested, may well have been the library of the school of Cos, treatises written by Hippocrates, his colleagues, and later disciples. The classic English translation is by Francis Adams, the country doctor of Banchory, Scotland, who, as a recreation from his arduous practice, translated Greek medical classics. The most complete and still the standard edition of the *Corpus* is that of Émile Littré in 10 volumes, the first volume of which appeared in 1839, the last in 1861. Littré had completed his medical studies but, instead of becoming a practicing physician, became a great classical philologist. This linguistic superiority based on a medical background explains in great measure the excellence and the popularity of Littré's translation. The physician in his study, browsing over this translation, always finds something to interest and to surprise him. The amazing clinical descriptions of tetanus, of mumps, of pneumonia, of epilepsy, of Cheyne-Stokes respiration, written 2000 years before either Cheyne or Stokes were born, these all amaze him. As he reads the directions for eliciting succussion in hydropneumothorax, the conditions under which one hears râles, a masterful description of the pleural friction rub ("it squeaks like a leather strap"), the method of inducing artificial pneumothorax in pulmonary disease (supposedly discovered by Forlanini in 1894), he recalls the old saying, "The ancients have stolen our best thoughts."

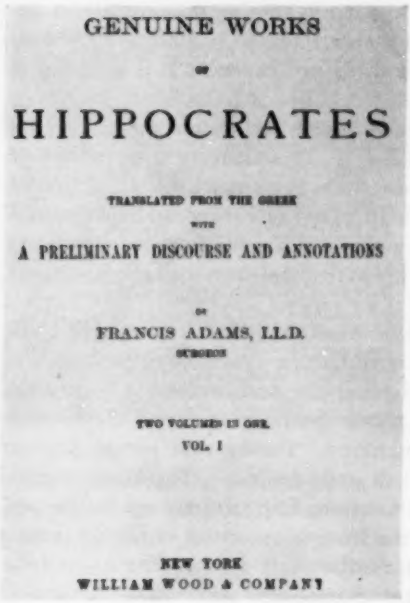
When we speak of the ancient physicians, we invariably think of two—Hippocrates and Galen—and often think of them as contemporaries although Hippocrates died 500 years before Galen was born. While there have been discussions for centuries regarding the authenticity and authorship of the *Hippocratic Corpus*, there is no doubt that most of the medical treatises attributed to Galen were actually written by him. The principal problem is to decide how many books Galen actually wrote. His extant writings on medicine aggregate 2,500,000 words, and at least half as

many have been lost. However, supposedly lost works turn up occasionally in unsuspected places. In 1931, an Arabic translation of Galen's *On Medical Experience*, written by Galen when he was 21, was discovered in Istanbul. It is doubtful if anyone has read all of Galen's works—the task would be too formidable.

The most widely read of Galen's works was probably his *De usu partium corporis humani* (*On the Use of the Parts of the Human Body*). This amazing compendium of anatomy and physiology, although it contains errors, is a remarkable collection of accurate observations, which justify Galen's title as the Father of Experimental Physiology and as one of the earliest physicians to put his questions to nature and await her answers. For 14 centuries, this work was the final answer to all anatomical and physiological questions.

During the long period known as the Middle Ages and called by some the Dark Ages, the earth seemed stayed in its rotation, with Europe remaining in darkness and the sun of progress and light shining brightly over the Arabian lands. Sarton has remarked, "Those ages were never so dark as our ignorance of them. Arabic was the scientific, the progressive language of mankind. During that period, anyone wishing to be well informed, up to date, had to study Arabic." The Arabs reintroduced into Latin Europe the works of Plato, Aristotle, Hippocrates, and Galen, and Christians, who learned Arabic at Córdoba, the leading university of Europe, translated the Arabic versions of the great Greek thinkers into Latin. The Arabs soon developed their own great philosophers, mathematicians, poets, and physicians, whose works dominated European learning for half a millennium. Avicenna (980–

Hippocrates of Cos. Statue found on Cos. Photo by author.


GENUINE WORKS

OF

HIPPOCRATES

TRANSLATED FROM THE GREEK

WITH

A PRELIMINARY DISCOURSE AND ANNOTATIONS

BY

FRANCIS ADAMS, LL.D.

SURGEON

TWO VOLUMES IN ONE.

VOL. I

NEW YORK

WILLIAM WOOD & COMPANY

Title page of Adams' translation of Hippocrates.

1037), one of the great Moslem thinkers, poet, philosopher, mathematician, astronomer, and physician, was the author of the *Canon of Medicine*, which Osler called "the most famous medical textbook ever written." It was a required text in European universities 600 years after his death. This enormous compendium of medical wisdom, containing more than a million words, was regarded in time as an infallible repository of wisdom and therefore became a stumbling block to medical progress.

For centuries anatomy made no progress. Galen's anatomy was the anatomy of the Greco-Roman, the Byzantine, the Arabian, and the medieval physicians of Europe. Much of it was incorrect because much of it was the anatomy of the ape, the pig, and lower animals, instead of the human body. More than 1300 years after the death of Galen, a bold young Belgian physician of 28, Andreas Vesalius, published his *De Humani corporis fabrica* (1543) (concerning the fabric of the human body, *not* of the ape or the pig or any lower animal). In this great work, Vesalius, while referring to the great Galen with respect, pointed out that he had made mistakes, which Vesalius proceeded to correct. The *Fabrica* is one of the truly great landmarks in the history of man's progress. Some have described it as the greatest book in the history of medicine since it described accurately, for the first time, the anatomy of the human body.

Nearly a century passed before William Harvey's *Exercitatio anatomica de motu cordis et sanguinis in animalibus* appeared in 1628. Harvey, educated at Cambridge and at Padua, was a mature man of 50 when his masterpiece was published in contrast to the youthful Vesalius, who was only 28 when the *Fabrica* appeared. Harvey is justly celebrated as the discoverer of the circulation of the blood. Others, in arm-

chair speculations, had theorized correctly about the circulation, but Harvey, by experiment, had proved his theory. Harvey not only discovered the circulation of the blood; he introduced experimental physiology to his own and succeeding generations, a science dormant since the death of its founder, Galen, more than 1400 years previously.

De sedibus, et causis morborum per anatomen indagatis of Giovanni Battista Morgagni, completed when the author was 79 years of age, marks the foundation of modern pathological anatomy. Morgagni, as Virchow pointed out, introduced anatomical thinking into pathology, localizing pathological lesions in definite organs. This great work is most interesting to read. The author begins each case history by describing the patient, his illness, his symptoms, and his death, often introducing human interest stories and sometimes piquant details. The autopsy is described in meticulous detail and an attempt made to correlate the symptoms and signs of the disease with the pathological findings. In the course of his vast experience over the years, Morgagni saw and described in *De sedibus* almost every pathological lesion with which we are familiar today.

The same year that *De sedibus* of Morgagni appeared, a young man of Vienna, Leopold Auenbrugger, published his *Inventum novum*, which describes the method and value of percussion in diagnosis. While Morgagni became famous overnight because of his book, Auenbrugger's little volume remained largely unnoticed until Corvisart's French translation made Auenbrugger famous 47 years later, the year before his death. The story that Auenbrugger came upon this discovery by remem-

كتاب القانون في الطب

لابي علي الشيخ الرئيس

ابن سينا

مع حل تاليفه وهو علم التشاف وعلم الطبيعي
وعلم الكلام

ROMAE,
In Typographia Medicea.
M.D.XCIII.

Title page of Avicenna's *Canon*, Arabic edition, printed in Rome, 1593.

Title page of first edition of Vesalius' *De Humani corporis fabrica*, 1543.

bering that he could tell the level of wine in a cask by thumping on the end of the cask is not apocryphal. In his *Inventum novum*, he mentions the method of tapping on the end of the cask.

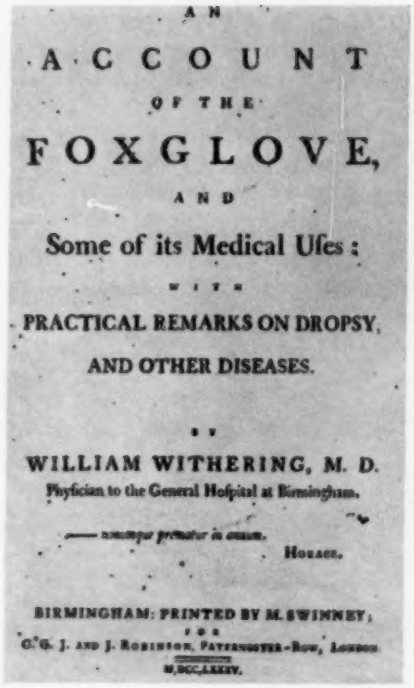
Title page of first edition of Harvey's *De motu cordis*, 1628.

JO. BAPTISTÆ
MORGAGNI
P. P. P. P.
DE SEDIBUS, ET CAUSIS
MORBORUM
PER ANATOMEN INDAGATIS
LIBRI QUINQUE.
OBSECTIONES, ET ANIMADVERSIONES, NUNC PRIMUM EDITAS COMPLECTUNTUR PROPEMODUM INNUMERAS, MEDICIS, CHIRURGIS, ANATOMICIS PROFUTURAS.
Multiplex præfixus est Index rerum, & nominum accuratissimus.
TOMUS PRIMUS
DUOS PRIORES CONTINENS LIBROS.
VENETIIS,
MDCCLXI
Ex Typographia Remondiniana.
SUPERIORUM PERMISSU, AC PRIVILEGIO.

Title page of first edition of Morgagni's *De sedibus*, 1761.

LEOPOLDI AUENBRUGGER
MEDICINÆ DOCTORIS
IN CÆSAREO REGIO NOSOCOMIO NATIONUM
HISPANICO MEDICI ORDINARII.
INVENTUM NOVUM
EX
PERCUSSIONE THORACIS HUMANI
UT SIGNO
ABSTRUSOS INTERNI
PECTORIS MORBOS
DETEGENDI
VINDOBONÆ,
TYPIS JOANNIS THOMÆ TRATTNER, CÆS. REG. MAJEST. AULÆ TYPOGRAPHI
MDCCLXI

Title page of first edition of Auenbrugger's *Inventum novum*, 1761.



AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.

Phyſician to the General Hoſpital at Birmingham.

—— nonumque prematur in annum.

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;

FOR

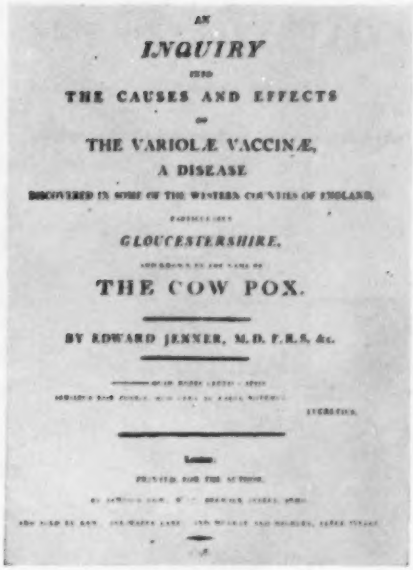
G. G. J. AND J. ROBINSON, PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

Title page of first edition of Withering's *An Account of the Fox Glove*, 1785.

In the closing years of the eighteenth century there appeared two works that profoundly influenced medical practice—William Withering's *An Account of the Fox Glove and Some of its Medical Uses* (1785) and Edward Jenner's *An Inquiry into the Causes and Effects of the Variolae Vaccinae* (1798). The former marks the introduction of digitalis into the practice of medicine; the latter describes the method of preventing that centuries-old pestilence, smallpox. Both were, in a sense, chance discoveries, but, as Pasteur was to point out later, "In the fields of observation, chance favors the prepared mind." Withering heard of an old woman in Shropshire who brewed a tea that cured dropsy. A skilled botanist, he felt sure after securing the formula that the foxglove was the active ingredient; after administering it for 10 years to his patients, he reported his results. The title page of Withering's book carries a quotation from Horace: "*Nonunque prematur in annum*" ("Let it be suppressed for nine years"). While this advice was given to an aspiring young poet who had read his verses to Horace, it would be good advice for many authors of today.

Jenner's inspiration came from a young dairymaid who consulted him for a headache and, when he suggested that possibly she had smallpox, answered: "I cannot take smallpox, for I have had cowpox." This chance remark was followed by years of study and experiment by Jenner.



AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

Title page of first edition of Jenner's *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ*, 1798.

René Théophile Hyacinthe Laënnec's *De l'auscultation médiate* (1819) marks the introduction of auscultation into the practice of medicine. The physician of today can scarcely imagine the practice of medicine without auscultation. The story of

DE

L'AUSCULTATION

MÉDIATE

OU

TRAITÉ DU DIAGNOSTIC DES MALADIES

DES POUMONS ET DU CŒUR,

FONDÉ PRINCIPALEMENT SUR CE NOUVEAU

MOYEN D'EXPLORATION.

PAR R. T. H. LAENNEC,

D. M. P., Médecin de l'Hôpital Necker, Médecin honoraire des Dispensaires, Membre de la Société de la Faculté de Médecine de Paris et de plusieurs autres sociétés nationales et étrangères.

Τοῖσιν δὲ μέγας ἔχθρὸς ὁ κόμπος οὗτος ἐν ἰητροῖσιν ἐστὶν οὐ δοκέοντα εἰδέναι.

Pouvoir explorer est, à mon avis, une grande partie de l'art. Hipp., Epid. VII.

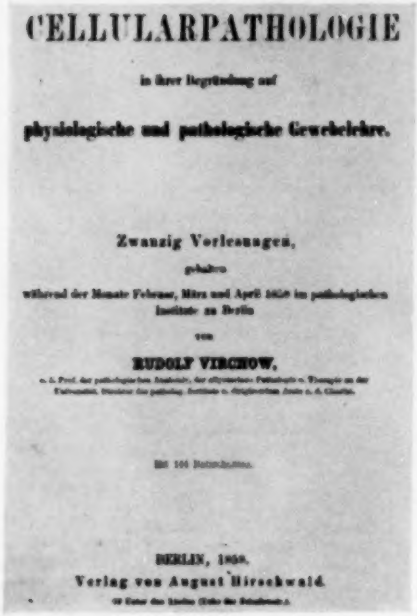
TOME PREMIER.

A PARIS,

CHEZ J.-A. BROSSON ET J.-S. CHAUDÉ, Libraires, rue Pierre-Sarrazin, n° 9.

1819.

Title page of first edition of Laënnec's *De l'auscultation médiate*, 1819.



CELLULARPATHOLOGIE

in ihrer Begründung auf

physiologische und pathologische Gewebelehre.

Zwanzig Vorlesungen,

gehalten

RUDOLF VIRCHOW,

BERLIN, 1858.

Verlag von August Hirschwald.

Title page of first edition of Virchow's *Cellularpathologie*, 1858.

the discovery of the stethoscope is well known. Laënnec, on his way to see a patient, saw a group of children playing in the court of the Louvre, one youngster scratching a long pole with a pin while the other children, listening at the other end of the pole, yelled every time he scratched. When Laënnec reached the patient's bedside, he rolled up a sheet of cardboard into a cylinder, placed one end to his ear, the other on the patient's chest, and thus the stethoscope was discovered. What is perhaps not so well known is that Laënnec had first become interested in auscultation when he read Hippocrates' description of the râles heard when one listened with the ear against the patient's chest. In his book, Laënnec taught how to diagnose pulmonary tuberculosis, which marked the beginning of an aggressive campaign against the "captain of the men of death."

Rudolf Virchow, with his *Cellularpathologie* (1858) and his doctrine, "omnis cellula e cellula," brings us into the modern epoch of medicine. Morgagni introduced the anatomical concept into pathology; Virchow refined the concept by showing that disease attacks the cells of the organ. Virchow was the personification of the spirit that led to spectacular advances in pathology, embryology, physiology, bacteriology, and chemistry, many of which were the triumphs of his colleagues and fellow countrymen.

To these great books, William Osler's *Principles and Practice of Medicine* (1892) should be added. This work, comprehensive, accurate, written with charm and lucidity, very warm and very interesting to read, had a remarkable success. A generation of American physicians were nurtured on this book, and the author had the satisfaction of seeing more than 100,000 copies sold. It had a profound influence on

William Osler working on *Principles and Practice of Medicine*. (From Cushing, H.: Life of Sir William Osler, New York, Oxford University Press, 1925.)

the medical practice of its day and, quite by chance, an even greater indirect influence on medical education and public health. In the summer of 1897, Mr. F. T. Gates, a friend and adviser of John D. Rockefeller, bought a copy of Osler's *Principles and Practice of Medicine*. "It is one of the very few scientific books that are possessed of high literary quality," wrote Gates. "There was a fascination about the style itself that led one on, and, having once started, I found a hook in my nose that pulled me from page to page, and chapter to chapter until the whole of about a thousand large and closely printed pages brought me to an end." But "he had no word of comfort . . . About all that medicine up to 1897 could do was to suggest some measure of relief, how to nurse the sick, and to alleviate in some degree the suffering. Beyond this, medicine as a cure had not progressed." Gates was greatly distressed; he had several interviews with Osler, became fired with the challenge of medicine, and transmitted his enthusiasm to Rockefeller. Thus the Rockefeller Institute for Medical Research and the Rockefeller Foundation became realities. When one considers the vast scope of the Rockefeller benefactions in medical research, medical education, and public health and recalls the stimulus that produced these colossal works of mercy, it must certainly be acknowledged that this book of Osler's was one of the most influential books of its century.

With this masterpiece of Osler we close our survey, covering a period of more than 3000 years. The books described have certainly had a decisive influence in charting the course of medicine over this long period.

William Shakespeare, M.D.

Anthony Ruggiero, M.D.

ELLENVILLE, N. Y.

> Those she has
> Will stupefy and dull the senses awhile;
> Which first, perchance, shall prove on cats and dogs,
> Then afterward up higher; but there is
> No danger in what show of death it makes,
> More than locking up the spirits a time,
> To be more fresh, reviving.
>
> *Cymbeline*, Act I, scene v

> I will try the forces
> Of these thy compounds on such creatures as
> We count not worth the hanging,—but human—
> To try the vigour of them and apply
> Allayments to their act, and by them gather
> Their several virtues and effects.
>
> *Cymbeline*, Act I, scene v

Besides being the world's greatest playwright, a poet, and a philosopher, William Shakespeare possessed medical knowledge, familiarity with medical and surgical practices of his time, and foresight in relation to the healing art, as to other areas of life, which arouse continuous wonder in a thoughtful mid-twentieth-century reader, especially one who is himself a practitioner of that art.

The wonder is even greater, since Shakespeare used his knowledge in a most unusual way, with results that continue to be both entertaining and informative. He observed details and described them in deft and memorable phrases, from "the great wart on my left arm" to the covering of the brain by the pia mater. He welded his knowledge of medicine as practiced in his time into majestic poetry for the enjoyment and the uplift of both the intellectual and the almost illiterate, the elite and the lowly, not only of his time but of all time after him so far as civilization may reach and last.

During the last century several physicians, notably Bucknill[1] and Wainwright,[2] have made studies of the evidence of medical knowledge in the Shakespearean writings. But medicine was not the only science in which Shakespeare displayed far more than ordinary knowledge. His phrases or allusions denoting a grasp of astronomy, physics, psychiatry, and botany also have inspired special studies. He seems to have been familiar with and to have understood all science as well as art of his day; his references are those of a sure mind.

This paper, supplemented by quotations from Shakespeare's works dealing with or referring to medicine, medical practice, surgery, and their collateral specialties, attempts to show the extent and quality of his medical knowledge from a modern standpoint as well as against the background of the Elizabethan era, and also to account for his medical knowledge. His son-in-law was a physician, who himself

did some writing for publication. Having a physician in the family may have been a help, but it would hardly explain the strong current of medical knowledge and allusion that runs through all Shakespeare's plays, early and late. Some medical references are subtle, others unmistakable. In reading and rereading the works of William Shakespeare I have listed at least 400 passages containing medical allusion or terms. A more careful analytical study probably would bring the list to almost 500.

William Shakespeare was well equipped from the start, for his own profession and for the understanding of others. He possessed the mind of an intellectual giant and was a man of prodigious learning (though he carried it lightly) and infinite versatility; he absorbed all information within his reach, and often reached out for more, was interested in everything that comprised his world or that could be known about the world before him and in the future. The splendor of the court and the gossip of the alehouse were alike important to him, and just as important was everything in between, including medicine and related matters.

At the time Shakespeare lived (1564–1616) physiological knowledge was still incomplete and inaccurate, medical knowledge was scant and unscientific, surgery was undertaken with trepidation, born of ignorance—and was as likely to be done by the barber as by the surgeon.

Apart from the innovations of the very early Greek physician and philosopher Galen, pathology was still, in Shakespeare's time, rooted in the ancient theory of the four fundamental principles or elements of the natural world: air, fire, water, and earth. Each element had its own quality or character: cold, heat, moisture, or dryness. As man was part of the natural order, he partook of these qualities, and the blending of any two produced his "complexion" or, as we say today, "temperament." Furthermore, each complexion or temperament had its own associated "humor."

Diagnosis of disease often was carried out in ridiculous manner, as satirized by Shakespeare and later also by the great French playwright Molière. For example, the cultist would diagnose by glancing at a sample of voided urine. In view of such absurd practices, it is no wonder that mortality rates were staggering.

Shakespeare was well acquainted with actual diseases and their treatment. He described many that we recognize with ease from his poetic words: epilepsy, gout, lues, psychosis among them.

Contagious diseases were believed to emanate from the South, near the Equator. "The South wind doth corrupt and make for evil vapours . . ." wrote the bard. Syphilis, prevalent throughout Europe, was called by some "the French disease" (morbus gallicus) and by others, "the Neapolitan disease," because it was so common in those places. Gout often plagued the rich, as Shakespeare testifies, but although it was attributed to their eating habits, they did nothing to avoid or overcome it. The quantity of food consumed by the average Elizabethan, if he could afford it, was enormous.

The well-bred and wealthy Londoner of the time of Queen Elizabeth I and of Shakespeare was not too careful about his personal hygiene, but he cared for his teeth three times a day. These received special attention—they were picked as well as washed. The wooden toothpick was acceptable, but the aristocrat invariably pos-

sessed an instrument of gold or silver. The celluloid pick of the Victorian era and of the early twentieth century in America—the type your grandfather was likely to produce from his vest pocket after a meal—was not available in Elizabethan times, and would not have seemed good enough anyway.

Certain aspects of hygiene were important to the Elizabethan, but these did not include sanitation. Sanitary conditions were wretched everywhere, and worst, of course, in a city. Excretions and refuse either were heaped in piles that drained away as it rained or were dumped into the nearest stream, in London into the Thames River.

We can see, though they could not, why "plagues" and other diseases spread so rapidly and carried off an appalling number of victims. People feared the "scourges" but regarded them as inevitable. Progress in this area began during Shakespeare's time. Sir John Harington invented the water closet in 1596, but it was not perfected until 182 years later.

Inadequate fuel and heating facilities constituted a further hazard to health and comfort. Coal was in common use for cooking and for industrial purposes, but not for domestic heating. However, the better homes did have an abundance of light and sunshine, if there was any.

Bloodletting was the first and most common treatment for any ailment; purging of the digestive system was a close second, regardless of the ability of the patient to withstand either treatment or of any special condition or circumstances that might suggest caution. All kinds of empirical and irrational compounds were administered, most of them weird, many of them actually harmful.

Tobacco served the Elizabethan not only for the pleasure of smoking but also as a fumigant and a narcotic. In an era without anesthetics, mandrake, too, was used as a narcotic. Steeped in wine, it was administered when surgeons decided to "cut, saw or take off a limb."

The Queen had three personal physicians, Drs. Huick, Julio, and Bayley, and each of the three presented her with identical medication: green ginger, preserved. Although the Elizabethans did not know about vitamins as such, the British Navy of the time used "scurvy grass." Most ships bent on a long voyage carried a large supply of this vegetation as protection against the "sailor's disease," which arose from lack of fresh vegetables and fruit that contained vitamin C.

The curative powers of herbs were of the greatest importance and interest to Elizabethans. Apothecaries were the specialists in mixing potions, but the apothecary and the physician had much competition in the preparation and use of herbs, for everyone who had a patch of ground grew them. The grocer would copy or imitate the prescriptions of a physician and sometimes superseded both physician and druggist. The barber or the dishwasher might grow his own herbs and concoct medicaments with little or no knowledge of their potentialities. Lay persons grew their own for self-treatment—and the practice of medicine was almost wholly in the hands of quacks, which caused many bitter feelings and much distrust among the people.

But the herb fad did have some good features. Books on herbs were as important to the literate Elizabethan gentleman as a cookbook is today to an American house-

wife. The cultivation and use of herbs became a hobby, and in every home rose water was distilled for use therapeutically as well as for a body perfume.

One of the astonishing things about Shakespeare's writing is the apparent knowledge of the blood and the circulatory system, imperfect as it was. Shakespeare could not have known of Harvey's circulation theories because these were expounded in the Lumleian lectures in 1616, a few weeks before Shakespeare died.

For one thing, any worth-while publication was required reading for anyone who would be well informed or considered fashionable in that age. An important cultural medium of the time was literature. Printing was still a limited art, and to get into print, especially between book covers, a man had to have something worth while to say. The curtain of ignorance was lifting with increasing momentum, and William Shakespeare was a prototype: he represented an emphatic concentration of the desire to know, which actuated almost everyone of his time in the stratum of society in which he moved. Not many, however, understood what they read as Shakespeare did; fewer still could make any practical use of it. Whether or not he could make use of it in a medical way, Shakespeare could and did use his knowledge in a most effective manner. He made medical knowledge serve well his profession of playwright.

It may be assumed that Shakespeare already knew about Aristotle's thought that blood was elaborated from food in the liver, then carried to the heart, and finally sent through the body in the veins, and about the theory of the Alexandrian physicians, Erasistrastus and Herophilus, that the veins carried blood and the arteries carried air or "spirit." He must have known, too, that Galen had discovered that the arteries carried blood as well as vital air or spirit and that the blood moved through the body, that is, was not stagnant.

Thus, in a general and vague way, the idea of circulation had already come into use in relation to the blood when Harvey and Shakespeare were writing. But it was believed that there were two kinds of blood: one that flowed from the liver to the heart's right ventricle and from there to the lungs and on through the general system of veins, and the other flowing from the left ventricle to the general system through the arteries. It was questioned whether the heart had motor power and was capable of muscular contraction. And it was believed that "spirits" within the heart influenced its pulsations and the flow of blood.

The septum of the heart was considered pervious, allowing blood to pass from the right to the left side, until Vesalius ascertained—just in time to gain acceptance when Shakespeare was writing—that the septum was complete between the right and left ventricles, but Vesalius still believed that some kind of invisible pores permitted transfer of blood from one side of the heart to the other.

Then, in 1553 Servetus stated that there was a communication in the lungs by which blood passed from the pulmonary artery to the pulmonary vein. At about the same time Fabricius demonstrated the system of valves in the veins. A century later Malpighi demonstrated the capillary bed.

Harvey's contribution was, of course, the most significant. It involved eight points: Contraction of the heart squeezed blood into the aorta and pulmonary artery. Pulse is produced by filling of the artery with blood. There are no pores

in the septum. Blood in the arteries and the veins is the same. The mechanism of the right and left sides of the heart (ventricles, auricles, valves) involves reception and propulsion of liquid and air. Blood propelled through the arteries is not used but goes into the veins. There is no to-and-fro undulation in the veins but a constant flow from the distal parts to the heart. The dynamic point of the blood is the heart, not the liver.

If all this seems far removed from the bard of Avon, his poesy and dramatic telling of tales and recounting of legend and history, the relationship will appear more clearly with increased knowledge of the Shakespeare family and the social setting in which its most famous member lived and worked.

William Shakespeare was born in Stratford-on-Avon, April 23, 1564, the third child but first survivor of eight offspring of John Shakespeare and Mary Arden. Two girls, Joan and Margaret, who were born before William, died as infants. The younger children were Gilbert, born in 1566; Joanne, 1569; Anne, 1571; Richard, 1574; and Edmund, 1580. The father was elected mayor of Stratford in 1568, became chief high bailiff the next year, and later was an alderman. By occupation he was essentially a wool dealer and was a native of the river town in the midst of agricultural country not far from the wooded district of his wife's birth, the forest of Arden. He had a sound education, acquired in the free grammar school. His son William's education was begun when the boy was 7, and in one way or another it continued throughout his life, although his formal education ended early. In the autumn of 1582, when he was 18, William Shakespeare married Anne Hathaway of Shottery, a nearby hamlet, where her father was a farmer. She was eight years older than her husband. They had a daughter Susanna, baptized May 26, 1583, and two years later there were twins, Hamnet and Judith. These are, at least, the facts and dates that seem to me most acceptable in relation to a person and a family of whom there are few actual records and much controversy.

Susanna's marriage to a physician gave her father a close personal association with the medical profession, which possibly helped provide him with so many apt and knowing phrases, the sort of information that a playwright would scarcely be expected to have or to turn to poetic use. But was it William Shakespeare's association with medical men that brought his daughter into acquaintance with Dr. John Hall? And did Shakespeare's ability as a writer and his association with printers and booksellers prove useful to his son-in-law? Dr. Hall was to become a man of some literary facility as well as medical reputation.

The Halls lived in Stratford and had one child, Elizabeth. By that time Susanna's father needed to have no hesitancy about appearing in his ancestral town, which he had left as a young man.

There is at this period a long blank in our knowledge of Shakespeare's career. Ultimately he appeared in London, where he found employment for his energies and genius as actor and playwright. But his association with the theatre did not start that way, for he was first employed in menial capacities, perhaps even as a holder of horses at the stage door. However, recognition of his talents came with little delay. London acknowledged him an actor and a great writer—he wrote an average of two plays a year along with his acting.

Ben Jonson said Shakespeare lacked art, but John Milton wrote appreciatively of his "native wood-notes wild," and posterity has agreed with Milton. The everyday world, art, and science he had alike at his command. It was typical of him to leave no aspect of life unexplored, and laughter or tears came at his bidding from audiences as he combined knowledge and talent to entertain them.

Literature was a passport by which persons of the lower and middle classes in England, particularly in London, might rise and form friendships with the great. Shakespeare, with good family background, some formal education, and a great intellectual curiosity and capacity, rose far above his middle-class origin. He had a strong creative impulse and a memory in which were stored, apparently in orderly files ready for immediate use, innumerable technical expressions, every morsel of popular belief he had ever heard, everything of current or historical interest or consequence.

To appreciate or even to understand Shakespeare and his work one must know something of Elizabethan England, its way of life, its knowledge and lack of knowledge. Then can be recognized what an unusual talent Shakespeare had and yet how he fitted so well into his time and place.

William Shakespeare found London an enormously different environment than he had known near the Avon; to him, London was a place of great contrasts, which fired his imagination and offered him much opportunity. There were extreme degrees of wealth and poverty, beggars on one hand and courtiers on the other. Between them were the middle-class, self-respecting, sober merchants and their families. It was, however, a restless middle class, with a desire to travel. These people were possessed of a deep love for independence, but distrustful of and disliking actors and their theatres. London itself was so straitlaced that an ordinance compelled actors to erect their buildings on grounds outside the city's control. There were in Shakespeare's time several attempts to suppress play acting altogether. But across the Thames, a banner flying from a theatre turret would announce a performance, and Londoners went by bridge or boat to see the play.

London streets were narrow, poorly paved, and wretchedly lighted, if at all. Many persons who ventured forth at night had a servant lead the way with a torch, called a "link." But the Thames afforded London a majestic highway spanned by a magnificent bridge. It was the best way to go from the city proper to Westminster. Queen Elizabeth was often seen on the Thames in her barge. By boat one could visit many interesting places, especially on the south bank, including the taverns and the theatres. And the river was always crowded with seagoing ships. At a Thames wharf, in Shakespeare's time, was docked a vessel of great interest, the "Golden Hind," the ship that Francis Drake had navigated around the world. But quite as typical of the time was the display of heads of executed criminals mounted on pikes above the gatehouse.

The city's population, within London's medieval walls, was about 100,000. On the outskirts, where there were lovely fields and beautiful woods, lived as many more people. Most important of the suburbs was Westminster, on the river's northerly bank. This, with its aura of royalty, attracted the nobility, and it became the nucleus of English culture. Fine buildings could be seen along that side of the

river. Parliament met in Westminster Hall, and the Queen's residence was not far away.

Queen Elizabeth reigned 45 years. This was an era of strong English nationalism, also an era of prosperity in which many Englishmen amassed fortunes. Many an Englishman enjoyed the new experience of comfortable leisure, and such circumstances combined to produce an atmosphere for self-expression in music and art of various kinds, especially the poetry of William Shakespeare and other great English writers. And the times provided much to think and talk about.

Added to his zest for living, the Elizabethan had a passionate regard for his sovereign as a great person. Shortly after Shakespeare's arrival in London, England astonished the world by defeating Spain's "Invincible Armada." Instead of a mere island, England became ruler of the seas. And English attitudes toward political freedom, religious reformation, and individual rights were strengthened.

Elsewhere other truths had been discovered and natural laws recognized. Copernicus advanced the theory that the sun and not the earth was the center of the universe. Columbus had discovered a new world, which changed the old world's outlook and literally gave man new horizons. The voyage of John Hawkins and Francis Drake opened opportunities for England in that new world and gave her naval and commercial supremacy.

The victories of Elizabeth's naval and military forces over Continental powers gave the Queen her great popularity at home.

Ultimately the Renaissance had its effect on England's culture. It was a nation intensely proud of its past and its present and confident of the future. Great and glorious literature was one of the results, and Shakespeare the most outstanding among the great literary men. Quite naturally, England, and Shakespeare, turned to the classics of earlier eras, and much was borrowed from Italian arts. But the results were thoroughly English.

Also thoroughly English was the way of life of the Londoner with whom Shakespeare associated. Rather oddly, the great meeting place was the nave of St. Paul's Cathedral. Until it was destroyed in the Great Fire of 1666, Londoners not only met friends there but did business in the shelter of its architectural grandeur. Late morning was the time to promenade at St. Paul's to display one's fine raiment, hail one's acquaintances, and transact various kinds of professional business. At one pillar a lawyer might be discussing a case, and at the next column might be artists with their canvases. Public secretaries were available there. Waiters and actors stood about and discussed food and plays. It was the place to hear about anything of current interest in London, the latest scandal or the best theatrical performance. Ben Jonson was among those who found it a good place to go, and undoubtedly Shakespeare did also. And while all this worldly activity was going on in the outer courts, divine worship might be in progress in the sanctuary of the cathedral.

The tavern was another center of London life. Merchants and aristocrats talked long over their wine at mid-day dinner, and afterward smoked and played cards or dice while they talked further of politics, the theatre, or England's latest victory. The Londoner of Shakespeare's time did enjoy the theatre and avail himself of its entertainment. Performances were in the afternoon (evening shows are a develop-

ment of the age of artificial lighting), and so diners in the city watched for or had messengers report on banners flying from theatre roofs on the south bank of the Thames.

The Globe Theatre had to be watched closely, even if it had a performance scheduled, because it was an open theatre and therefore subject to the weather.

The usual theatre admission price was a penny, equivalent to about 15 cents today, but at the aristocratic Blackfriars the charge was six pence ($1.00). Admission price merely gave the theatregoer the privilege of standing in the pit or possibly sitting in the top gallery. For a box the cost was a shilling ($2.00). At the Blackfriars the most fashionable persons were conspicuously seated on the stage itself, sometimes much to the inconvenience of the actors!

These were the way of life, the cultural atmosphere, the conditions that seem to have been so ideally suited to the intellect and temperament of William Shakespeare. Under these conditions, glorious literature flourished side by side with the concepts of individual freedom and religious reformation. And in this atmosphere Shakespeare added an almost universal knowledge to the not very extensive education he had received at Stratford and acquired an astonishing familiarity with the medical lore and practice of his time.

APPENDIX

Following are a few of the medical passages I have found in Shakespeare's writing, grouped in medical categories with occasional explanatory remarks or comment.

The Physician.

Medice, te ipsum.
Henry VI, Part II, Act II, scene i
[Physician, heal thyself.]

. . . But I consider,
By medicine life may be prolonged, yet death
Will seize the doctor too.
Cymbeline, Act V, scene v

Thou speak'st like a physician, Helicanus,
That minister'st a potion unto me
That thou wouldst tremble to receive thyself.
Pericles, Act I, scene ii

Medicaments.

With wholesome syrups, drugs, and holy prays
To make of him a formal man again.
Comedy of Errors, Act V, scene i

. . . made familiar
To me and to my aid the best infusions
That dwell in vegetables, in metals, stones . . .
Pericles, Act III, scene ii

Get me some of this distilled Carduus Benedictus,
and lay it to my heart. . . .
Much Ado about Nothing, Act III, scene iv

Take thou this vial, being then in bed,
And this distilled liquor drink thou off;
And presently through all thy being shall run
A cold and drowsy humor; for no pulse
Shall keep his native progress, but surcease
. . . . . .
Each part deprived of supple government,
Shall, stiff and stark and cold, appear like death. . . .
Romeo and Juliet, Act IV, scene i

Surgery.

He's a disease that must be cut away.
Coriolanus, Act III, scene i
[The need for amputation of a diseased part of the body]

This fester'd joint cut off, the rest rests sound; . . .
Richard II, Act V, scene iii

But we do lance
Diseases from our bodies. . . .
Antony and Cleopatra, Act V, scene i
[All three quotations refer to sound surgical procedures, used even today]

My leg is cut in two
I'll bind it with my shirt.
Othello, Act V, scene i
[First-aid treatment for laceration of the leg]

I'll fetch some flax and white of eggs
To apply to his bleeding face.
King Lear, Act III, scene vii

Orthopedics.

I fear, sir, my shoulder-blade is out.
A Winter's Tale, Act IV, scene iii
[A dislocation of the shoulder]

Our peace will, like a broken limb united,
Grow stronger for the breaking.
Henry IV, Part II, Act IV, scene i
[A callous formation is stronger than original bone]

Prosthesis.

. . . where a man may serve seven years for
the loss of a leg, and have not money enough in the
end to buy him a wooden one?
Pericles, Act IV, scene vi
[There were artificial limbs even then]

Ah! thus King Henry throws away his crutches
Before his legs be firm to bear his body.
Henry VI, Part II, Act III, scene i

Obstetrics.

. . . great bellied women
That had not a week to go. . . .
Henry VIII, Act IV, scene i
[A pregnant woman]

. . . he came into the world
Full fourteen weeks before the course of time.
King John, Act I, scene i
[A premature birth]

Macduff was from his mother's womb
Untimely ripp'd.
Macbeth, Act V, scene viii
[A Caesarean birth]

For I have often heard my mother say
I came into the world with my legs forward.
Henry VI, Part III, Act V, scene vi
[A breech presentation]

Circulation.

. . . he had a heart as sound as a bell.
Much Ado about Nothing, Act III, scene ii

Many will swoon when they look at blood.
As You Like It, Act IV, scene iii

Give me your hand and let me feel your pulse.
Comedy of Errors, Act IV, scene iv

My pulse, as yours, temperately keeps time
And makes as healthful music.
Hamlet, Act III, scene iv

Respiration.

Thou dost snore distinctly:
There's meaning in the snores.
The Tempest, Act II, scene i

Lend me a looking glass;
If that her breath will mist or stain the stone,
Why then she lives.
King Lear, Act V, scene iii

A whoreson cold, sir, a cough, sir, which I caught.
Henry IV, Part II, Act III, scene ii

O, I am out of breath in this fond chase!
A Midsummer Night's Dream, Act II, scene ii

He's fat and scant of breath.
Hamlet, Act V, scene ii

Neurology.

. . . these are begot in the ventricle of the memory,
nourished in the womb of the pia mater.
Love's Labour's Lost, Act IV, scene ii

. . . if you are sick at sea
Or stomach-qualm'd at land, a dram of this
Will drive away distemper.
Cymbeline, Act III, scene v
[Seasickness]

He fell down in the market-place and foamed at mouth and was speechless.
Julius Caesar, Act I, scene ii
[Epilepsy]

Thou cold sciatica,
Cripple our senators, that their limbs may halt
As lamely as their manners. . . .
Timon of Athens, Act IV, scene i
[Sciatica]

Methinks I see these things with parted eye,
When everything seems double.
A Midsummer Night's Dream, Act IV, scene i

Lord, my head aches! what a head have I!
It beats as it would fall in twenty pieces.
Romeo and Juliet, Act II, scene v
[A common ailment still, but possibly here meaning particularly migraine headache]

This is a strange repose, to be asleep
With eyes wide open; standing, speaking, moving,
And yet so fast asleep.
The Tempest, Act II, scene i
[Somnambulism]

Psychiatry.

Take heed, lest by your heat you burn yourselves. . . .
Henry VI, Part II, Act I, scene i
[The bad effect of an ill temper]

. . . for a light heart lives long.
Love's Labour's Lost, Act V, scene ii

This we prescribe, though no physician;
Deep malice makes too deep incision. . . .
Richard II, Act I, scene i

Fell into a sadness, then into a fast,
Thence to a watch, thence into a weakness,

Thence into a lightness, and by this declension
Into the madness wherein now he raves
And all we mourn for.
Hamlet, Act II, scene ii

It is a body yet distemper'd;
Which to his former strength may be restored
With good advice and little medicine; . . .
Henry IV, Part II, Act III, scene i

And melancholy is the nurse of frenzy:
Therefore they thought it good you hear a play
And frame your mind to mirth and merriment
Which bars a thousand harms and lengthens life.
Taming of the Shrew, Introduction, scene ii

More needs she the divine than the physician.
Macbeth, Act V, scene i

Extremity of griefs would make men mad; . . .
Titus Andronicus, Act IV, scene i

Good Lord, what madness rules in brainsick men,
When for so slight and frivolous cause
Such factious emulations shall arise; . . .
Henry VI, Part I, Act IV, scene i

Cure her of that
Canst thou not minister to a mind diseased
Pluck from the memory a rooted sorrow,
Rase out the written troubles of the brain,
And with some sweet oblivious antidote
Cleanse the stuff'd bosom of that perilous stuff
Which weighs upon the heart?
Macbeth, Act V, scene iii

Senility.

When sapless age and weak unable limbs
Should bring thy father to his drooping chair.
Henry VI, Part I, Act IV, scene v

Sans teeth, sans eyes, sans taste, sans everything.
As You Like It, Act II, scene vii

Have you not a moist eye? a yellow cheek? a white beard? a decreasing leg? an increasing belly? is not your voice broken? your wind short? your chin double? your wit single? and every part about you blasted with antiquity? and will you yet call yourself young?
Henry IV, Part II, Act I, scene ii
[Shakespeare had an unusual understanding of arteriosclerosis, senility, and schizoid reaction in old men, like King Lear]

Of Sundry Medical Association.

. . . the mark of my shoulder, the mole in my neck, the great wart on my left arm.
Comedy of Errors, Act III, scene ii

Welcome, gentlemen: Ladies that have their toes
Unplagued with corns will have a bout with you. . . .
Romeo and Juliet, Act I, scene v

And she taken upon her to spy a white hair on his chin.
Troilus and Cressida, Act I, scene ii

. . . their eyes purging thick amber tree gum.
Hamlet, Act II, scene ii

Guilderius had
Upon his neck a mole, and a sanguine star:
It is a mark of wonder.
Cymbeline, Act V, scene v

Let's see: come, if it be nothing, I shall not need spectacles.
King Lear, Act I, scene ii

Bid them wash their faces, and
keep their teeth clean.
Coriolanus, Act II, scene iii
[Hygiene]

A pox on this gout or a gout of this pox; for the one
or the other plays the rogue with my great toe.
Henry IV, Part II, Act I, scene iii
[A knowledge of syphilis and gout]

Most mischievous foul sin, in chiding sin:
For thou thyself hast been a libertine,
As sensual as the sting itself:
And all the embossed sores and headed evils,
That thou with license of free foot has caught,
Would'st thou disgorge into the general world.
As You Like It, Act II, scene vii
[Syphilis and its infection]

He is so shocked of a burning quotidian
tertian, that is lamentable to behold.
Henry V, Act II, scene i
[Malaria or ague]

Now the red pestilence strike all trades in Rome
And occupation perish.
Coriolanus, Act IV, scene i
[Typhus]

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BOOK REVIEWS

Insulin Treatment in Psychiatry: Proceedings of the International Conference on the Insulin Treatment in Psychiatry held at the New York Academy of Medicine October 24 to 25, 1958. EDITED BY MAX RINKEL, M.D., AND HAROLD E. HIMWICH, M.D. New York, Philosophical Library, Inc., 1959. Pp. 386. Price $5.00.

The current status of insulin therapy in psychiatry is reviewed in this interesting book, which contains the proceedings of a conference on insulin treatment held in 1958. An unusual feature of the book lies in the fact that opponents as well as proponents of the treatment are well represented and are permitted to express themselves freely.

Most of the contributors agree that insulin treatment is still an essential tool in psychiatry. A number of the participants emphasize the need for combined treatments, including insulin coma, electroshock, and ataraxics. Others point out that it is not a question of the superiority of drugs or insulin, but of suiting the treatment to the individual patient.

The various views expressed at the conference led to much lively discussion, which is recorded in the book.

Although in content this book is interesting and enlightening, it is replete with awkward phraseology in some of the foreign contributions, which might have been improved by more careful editing. In general, the format of the book is below standard.

The Royal Edinburgh Hospital for Sick Children, 1860–1960. DOUGLAS GUTHRIE with various contributors. Edinburgh and London, E. & S. Livingstone Ltd., 1960. Pp. 75. Price $4.25.

This book commemorates the centenary of the founding of the Royal Edinburgh Hospital for Sick Children. The distinguished author, Dr. Douglas Guthrie, who served as Surgeon to the Ear and Throat Department of the hospital from 1918 to 1936, is presently Consulting Aural Surgeon to the hospital. With the aid of a group of contributors, he has written an interesting account of the development of the hospital from the time when it first opened its doors on Feb. 15, 1860, to the present.

Illustrations are included of the original staff members, various buildings and wards, and other appropriate scenes in the history of the hospital. It is interesting to note that as early as 1871 the question was raised of "the admission of the ladies now studying Medicine in Edinburgh to attend the Wards and Dispensary practice" of the hospital; however, not until 1890 did the directors authorize the holding of clinics for ladies.

The various sources from which special donations were received by the hospital form a fascinating story in themselves. In 1872 the hospital received a donation of £18 0*s.* 6*d.* "from the disposal of a Rug sewed for the benefit of the Hospital by Madame Salomon and a few other ladies"; in 1907, £66 from the Committee of the

Edinburgh Cyclists' Fancy Dress Parade; and in 1946, £100 from the proceeds of Thankerton Sheep Dog Trials and £20 from the Rosewell Anti-Gloom Campaigners.

As portrayed in this book, the history of the hospital in the past 100 years has reflected a flexibility of staffing, equipment, and development that has been responsible for its continued growth and advancement. In looking ahead to the future, the hospital will certainly play an important part "in improving child health throughout the world."

A Short History of Scientific Ideas to 1900. CHARLES SINGER. New York, Oxford University Press, 1959. Pp. 550. Price $8.00.

That indefatigable historian of science, Dr. Charles Singer, whose erudition and industriousness are matchless in his field, has written a history of the ideas that steered the progress of science, from "the rise of mental coherence" in Mesopotamia, Egypt, Ionia, Magna Graecia, and Athens, until that "culmination of the mechanical view of the world," which began in 1800 and has fully blossomed in our time.

Based on the previous *A Short History of Science* by the same author, this new book is scholarly, enlightening, and entertaining. Against the background of succeeding civilizations, the author traces the evolution of scientific ideas: the great adventure of "the unitary systems of thought" in the Athens of Pericles; the second adventure, when science became divorced of philosophy, in the school of Alexandria; the "failure of inspiration" that made science "the handmaid of Practice" in Imperial Rome; the failure of knowledge in the Middle Ages, when Theology became the Queen of Sciences; the revival of learning through humanism and the attempt to return to classical antiquity in the Renaissance; the downfall of Aristotle and the new attempts at synthesis in the Baroque period; "the insurgent century," and the beginning, in 1700, of the enthronement of determinism and the mechanical world that led to the masterful role of science in our society.

Dr. Singer's prose, always lucid and coherent, though perhaps a little too crowded with facts (the penalty of the writer who knows too much of a subject and is limited in space and time in saying it) and 188 highly didactic diagrams and illustrations, tables and maps afford the reader a splendid vision of the ideas created by men that influenced mankind throughout the centuries and of the magnificent scientific heritage handed down to us by our predecessors. Dr. Singer possesses the enviable gift of making brief but uncannily accurate syntheses, like the one he makes of Descartes' ideas. His concept of science as the ultimate factor in modern society is vividly dramatized on the frontispiece of the book with a plate by Sebastien Le Clerc showing Louis XIV and his minister, Jean Baptiste Colbert, visiting the Académie des Sciences in 1671, which is "the earliest representation of a meeting of a learned society."—*Félix Martí-Ibáñez, M.D.*

the first of its kind...

A HISTORY *OF* NEUROLOGY

by Walther Riese, M.D.

Associate Professor of Psychiatry and Neurology; Chairman, Department of the History of Medicine, Medical College of Virginia, Richmond, Virginia
Consulting Neuropathologist to the Department of Mental Hygiene and Hospitals of the Commonwealth of Virginia

Here is a new approach to the history of neurology. With an historian's eye for the dynamic, the author has chosen to focus on "the great and lasting problems" that have remained inherent in man's endeavor through the ages to understand the functions of the nervous system and their disturbances. By concentrating on fact, thought, and theory, Dr. Riese has achieved a comprehensive picture of neurologic progress.

Dr. Riese traces the history of the doctrine of cerebral localization, its scope, limits, and different versions, both past and present. Other sections of special interest include those on the history of diagnosis, prognosis, and therapy in neurology; and a comprehensive treatment of the history of diaschisis or cerebral shock. Also included are invaluable sections: neurological chronology; list of journals specializing in neurology and neurological societies and associations.

This volume is one of a series devoted to the histories of various specialties and facets of medicine. Félix Martí-Ibáñez, M.D., who wrote the foreword to *A History of Neurology*, is the Editorial Director of the series, which includes Public Health and Ophthalmology.

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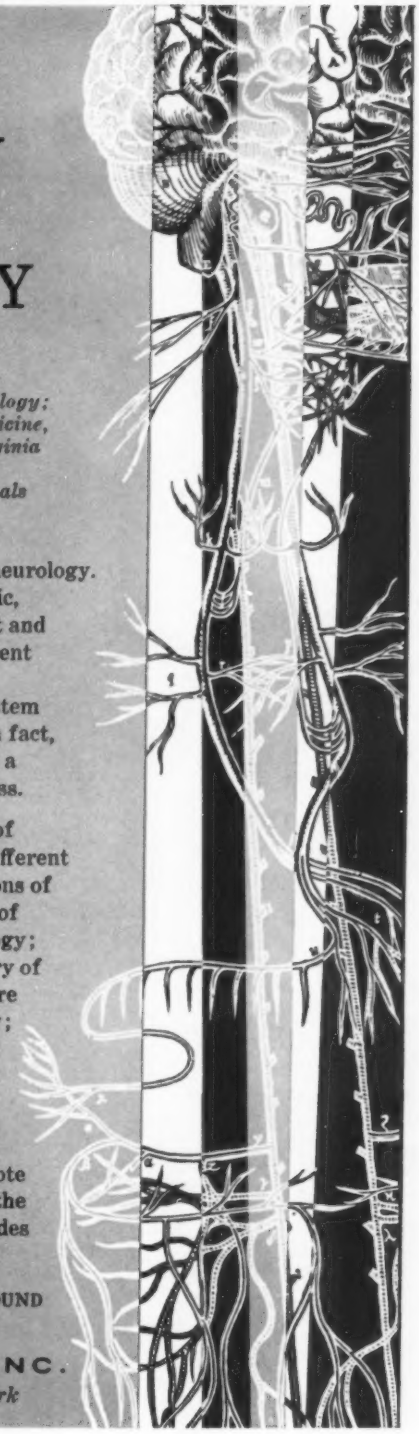

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A New MD Medical History...

A HISTORY *of* OPHTHALMOLOGY

by George E. Arrington, Jr., M.D.

Associate in Ophthalmology, Medical College of Virginia, Richmond, Virginia

A HISTORY OF OPHTHALMOLOGY provides an over-all view of ophthalmological progress through the ages. With scholarship and originality the author traces the thinking, of men known and unknown, that has made possible the technological advances of this science. Man's search for understanding of vision and its preservation is shown effectively in its relation to the history of civilization. The content of this book ranges from the period of prehistorical ophthalmology to the present day. In emphasizing the effect of related sciences, philosophy, and human culture upon ophthalmology, Dr. Arrington offers new insight into his subject. Appropriate attention is given the ascendancy of modern ophthalmology including an evaluation of its current trends in the light of the future. It is a book of interest to ophthalmologists, general practitioners, and students.

This volume is one of a series devoted to the histories of various specialties and facets of medicine. Félix Martí-Ibáñez, M.D., who wrote the foreword to A HISTORY OF OPHTHALMOLOGY, is the Editorial Director of the series, which includes books on Public Health and Neurology.

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